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BULLETIN

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Original Articles by

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HEADACHE:
ITS ETIOLOGY AND MANAGEMENT

Transcription of a Panel Meeting

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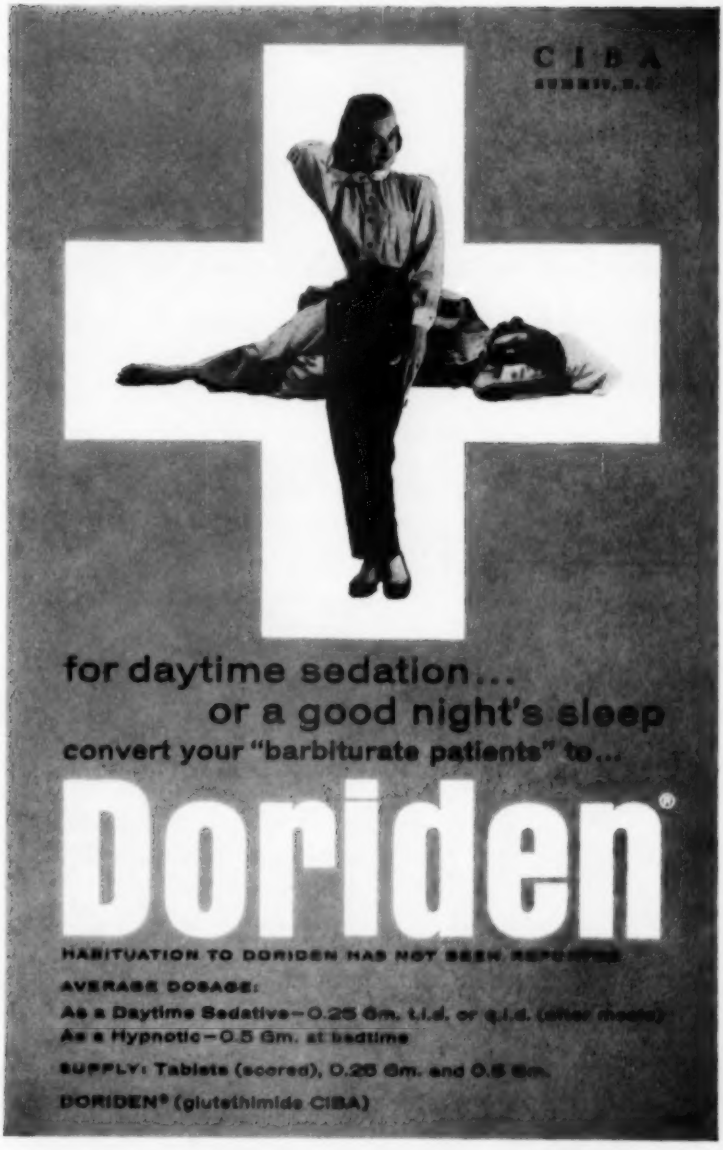
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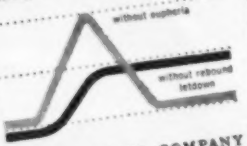

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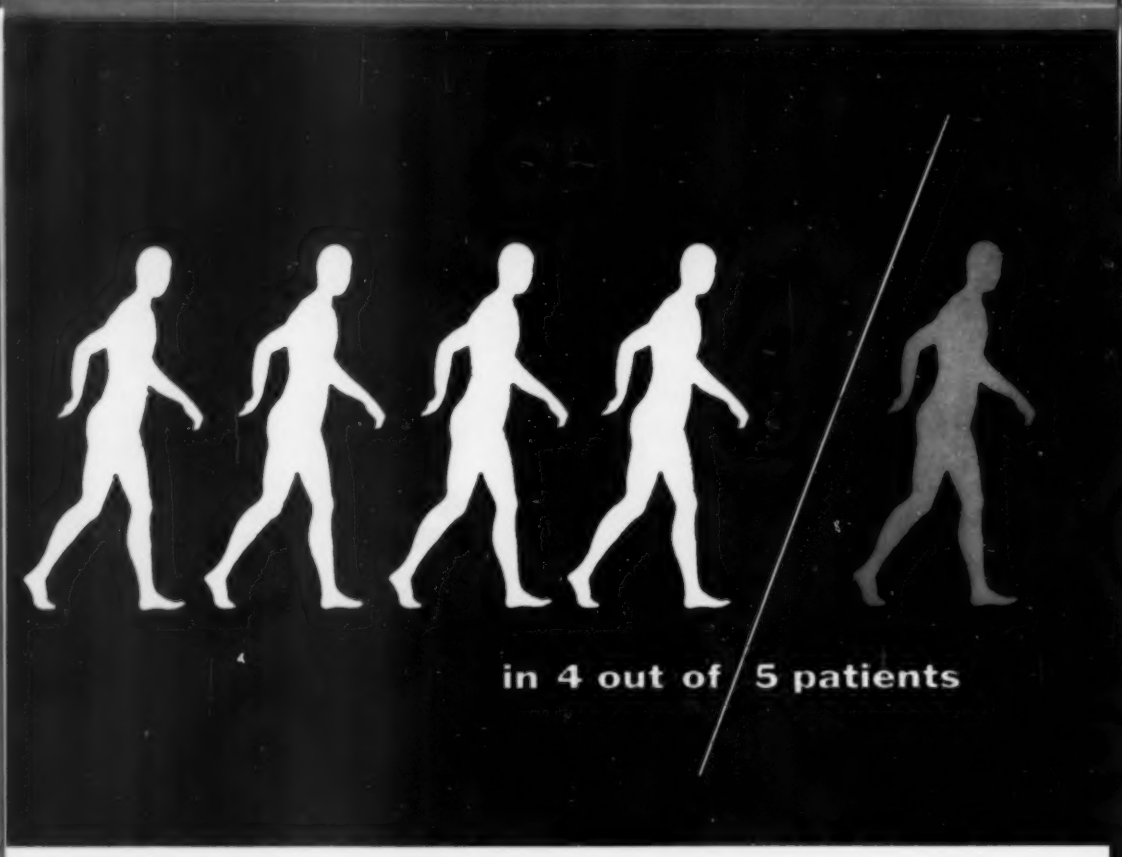

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1. Winsor, T., Humphreys, P.: Angiology *3*:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. 52:2012 (Aug. 15) 1952.
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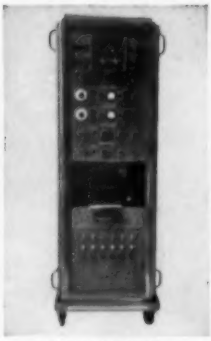

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1. Johnston, R.L.: J. Indiana St. M.A. 46:869, 1953. 2. McHardy, G., and Browne, D.: Southern M. J. 45:1139, 1952.

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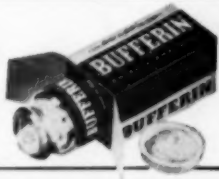

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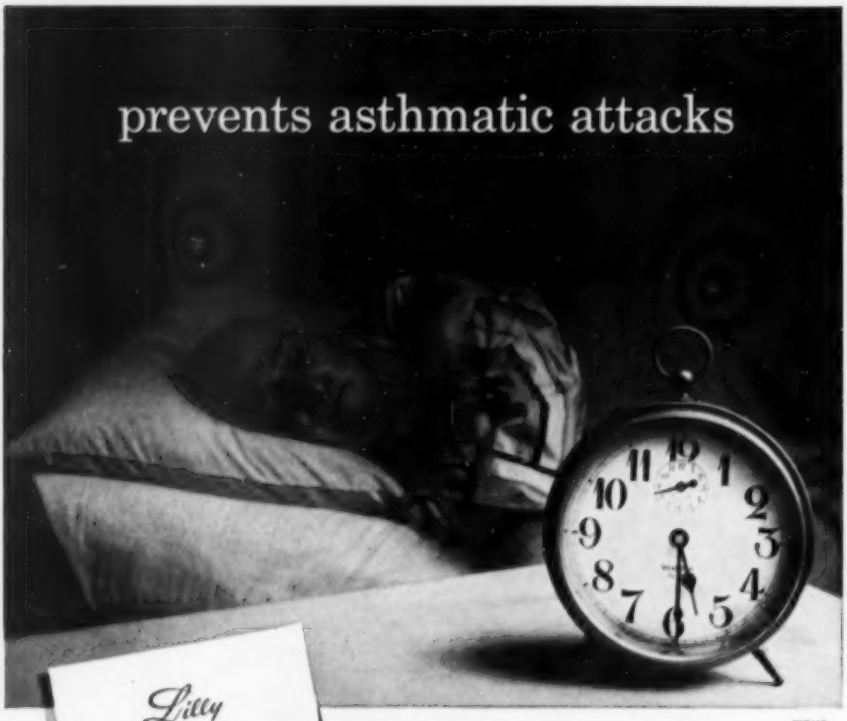

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 31, NO. 11 NOVEMBER 1955

APPROACHES TO THE CHEMOTHERAPY OF VIRAL DISEASES*

FRANK L. HORSFALL, JR.

Member, The Rockefeller Institute for Medical Research; Physician, Hospital of the Institute

EFFECTIVE chemotherapy for numerous bacterial infections is of course a well established fact. Certain concepts which have arisen from the study of antimicrobial substances may bear on efforts to develop effective chemotherapy for viral infections. A brief appraisal of the basis for these concepts seems desirable as an introduction to this discussion.

All of the substances that are useful in the treatment of bacterial infections have one property in common. Each of these modern chemotherapeutic substances leads to a reduction in the number of susceptible bacteria in the infected tissue. This is the effective mechanism through which the sulfonamides, penicillin, streptomycin and the tetracyclines exert beneficial effects on various diseases caused by bacteria. In each instance, the reduction in the number of bacteria is the result of an effect upon the rate of growth of the microorganism. Although the biochemical mechanisms are not identical and different chemotherapeutic drugs affect different bacteria in distinctive ways, the end result is the same. The rate of growth of the microbe is diminished and the production of

* Presented at the 27th Graduate Fortnight of The New York Academy of Medicine, October 29, 1954.

more bacteria is retarded. When the rate of growth is reduced enough to be lower than the rate of death or destruction of the microbe, the number of bacteria in the infected tissue decreases. Only when this result is produced are chemotherapeutic compounds effective in the treatment of bacterial infections.

If the number of bacteria is not diminished by the drug, the infection continues unabated and no response to the use of the antimicrobial compound is seen. As is well known, certain bacterial infections are not favorably affected by chemotherapeutic drugs which are highly effective in other bacterial infections. For example, penicillin is not effective against most infections caused by gram-negative bacilli. The reason for this is that penicillin has but little effect upon the rate of growth of such bacteria. Similarly, the loss of a therapeutic effect during the course of treatment is explained on the same grounds. Bacteria may become resistant to the growth-retarding effect of an antimicrobial compound during chemotherapy. Resistant bacteria are those that are able to grow in the presence of a compound that previously prevented growth. When resistant bacteria appear during an infection, the number of bacteria in the infected tissue increases despite continued use of the drug, and clinical evidence of disease reappears. Because the compound now fails to retard growth of the bacteria, the therapeutic effect is lost.

The development of the concept that effective chemotherapy in bacterial diseases is dependent upon reducing the rate of growth of the infecting organism may have importance for chemotherapy in viral diseases. Although viral infections are different from bacterial infections in a number of aspects, both kinds of infection have one common feature. Neither bacterial nor viral infections develop unless the infective agent multiplies in the host tissue. In both cases, clinical signs appear when the number of infective organisms in the invaded tissue becomes large. Infection either with viruses or bacteria is dependent upon multiplication or reproduction of the infecting agent and does not develop in its absence.

Not only is the fact of multiplication of the infecting agent essential to the development of infectious disease, but also the rate of multiplication is important. As was stated earlier, sufficient reduction in the rate of bacterial growth by a chemotherapeutic substance leads to eventual cure of the disease. In addition, so-called avirulent viruses fail to cause manifest disease, even though they induce an inapparent infection, because

they reproduce more slowly than fully virulent viruses.[1-3] As a direct result of the slower rate of reproduction, the number of virus particles in the infected tissue is smaller and obvious clinical signs of disease do not develop. This property of certain avirulent viruses has been of great benefit to human beings. Smallpox and yellow fever vaccines, for example, do not lead to frank virus diseases because the active viruses they contain multiply at a reduced rate.

Because chemotherapeutic substances which diminish the rate of bacterial growth are effective in the treatment of bacterial infections, it seems probable that compounds which inhibit the rate of virus reproduction should be effective in the treatment of virus infections. This idea has formed the basis for much research on chemotherapy in virus infections during recent years, and has been a major premise to which those in our laboratory have held for some time.[4, 5] The experimental results that have been attained thus far have strengthened the view that this approach to the chemotherapy of virus diseases merits continued exploration.

One may ask why, in the light of the number of highly effective substances available for the treatment of bacterial diseases, has there been so much difficulty in finding substances equally effective in the treatment of virus diseases? It is well known that except for the diseases caused by the psittacosis-lymphogranuloma group of agents, none of the virus diseases of man is strikingly altered by available chemotherapeutic drugs.[6] The answer to this question is not that small effort in a few laboratories has been expended on the problem. In fact, a great amount of effort has been exerted in many highly competent laboratories. Enough success has been achieved in experimental virus infections in animals to warrant still greater effort. The major difficulty has not been to find substances that inhibit virus reproduction in some susceptible host. A number of such substances are now known.[7, 8] The chief problem is to discover substances that will restrict virus multiplication in human beings without at the same time causing damage to the patient.

The single feature which makes viruses so different from bacteria is not their very small size, but their unusual means of reproduction. They are entirely unable to reproduce except when inside susceptible, living host cells. Viruses are the most absolutely parasitic of all infectious agents and only from the tissue cells they enter can they obtain everything they need for reproduction. To inhibit their reproduction it is

necessary to retard intracellular processes, and this fact immediately raises a major difficulty. That compounds active against extracellular viruses cannot be expected to be useful in the treatment of virus diseases is now clear. The most ideal substance for an extracellular attack on viruses is specific antibody, but there is abundant evidence that immune sera are of no value in the therapy of virus diseases.[6] Most workers interested in chemotherapy are no longer concerned with the possibility of an extracellular attack on viruses. Current work in the field is directed chiefly toward modifying the intracellular reproduction of these agents.[9,10]

It is not difficult to alter the rate of virus multiplication in experimental animals. Mild damage to infected host cells, produced by almost any means, results in some reduction in virus reproduction. Many compounds are known which will produce this effect.[7,8] Clearly, the more damaging a compound is for host tissue, the less likely it is to be useful as a therapeutic agent. If the substance is sufficiently damaging to infected tissue, the treatment can cause results worse than those produced by the untreated disease.

What is desired in the chemotherapy of virus infections are substances which affect some intracellular processes that either are specially required for virus reproduction or are used at a more rapid rate by the virus than by the infected host cell. This is a large problem and its solution is especially difficult because of the incompleteness of knowledge of the mechanism of virus reproduction. A variety of approaches is being employed in different laboratories, and there is no way to determine which is the most likely to succeed. In the end, that approach which yields the most effective substances, active in the largest number of virus diseases, will be the most beneficial. For the reasons indicated earlier, we adhere to the view that compounds which inhibit intracellular virus reproduction are those of interest and possess the potential of becoming models for useful chemotherapeutic substances.

Laboratories in a number of large industrial organizations and in numerous academic institutions have tested many thousands of substances against one or another virus infection in various experimental animals or tissue culture systems. Although the great bulk of substances has shown no significant inhibitory activity, a number of substances have been found which do inhibit virus multiplication.[7,8] Among these are some which appear highly active, for very small quantities inhibit

TABLE I—INHIBITION OF INFLUENZA VIRUS MULTIPLICATION BY BENZIMIDAZOLE DERIVATIVES

Compound		*Host*	*Influenza B virus multiplication*
	Mg.		*Per cent of Control*
DRB*	0.016	Tissue culture	1
"	4.0	Chick embryo	<3
"	4.0†	Mouse	9
TRB**	0.002	Tissue culture	1

* DRB = 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole.
** TRB = 4,5,6- (or 5,6,7-) trichloro-1-β-D-ribofuranosylbenzimidazole.
† Per day.
Data from I. Tamm et al.[15] in *J. exp. Med. 99:227*, 1954; and I. Tamm[16] in *Science 120:847*, 1954

the reproduction of certain viruses in host tissue cells. A few substances have been shown to retard multiplication even when given after the virus has entered the cell. Such substances qualify as the most interesting found so far and eventually may point the way toward useful chemotherapy.

During the past three years Igor Tamm and his associates in our laboratory have studied the relation between inhibitory activity and chemical structure of certain specially designed derivatives of benzimidazole. This area of investigation was chosen because of structural relations of some benzimidazole derivatives to part of the vitamin B_{12} molecule as well as to a constituent of nucleic acids. New compounds have been prepared in a series of chemical steps, in which each new step depended upon the structure-activity relations found in those preceding it. As a result of this carefully controlled approach it has been possible to produce new compounds which are highly active as inhibitors of influenza virus multiplication.[11-15] The most effective compound is over 700 times more active than benzimidazole itself.[16] The new compounds were synthesized by Karl Folkers and Clifford Shunk and their associates at The Research Laboratories of Merck and Company. The most active compound, designated TRB, has a ribose sugar at one position and three chlorine atoms at other positions in the benzimidazole molecule.[16] A few micrograms of TRB markedly inhibit influenza B virus multiplication in tissue culture (cf. Table I). This is

TABLE II—INHIBITION OF MUMPS VIRUS MULTIPLICATION BY BENZIMIDAZOLE DERIVATIVES

Compound		*Host*	*Mumps virus multiplication*
	Mg.		*Per cent of Control*
DRB*	1.0	Chick embryo	3
TRB**	1.0	" "	4

* DRB = 5,6-dichloro-1-β-D-ribofuranosylbenzimidazole.
** TRB = 4,5,6- (or 5,6,7-) trichloro-1-β-D-ribofuranosylbenzimidazole.
Data from I. Tamm[16] in *Science 120*:847, 1954.

the most potent inhibitor of influenza virus reproduction that has been discovered to date. In addition, this substance inhibits the multiplication of mumps virus in the intact chick embryo[16] (cf. Table II).

Extensive studies on an almost identical substance, designated DRB, which contains two rather than three chlorine atoms, revealed some highly interesting properties.[15] This compound also is a potent inhibitor of influenza A or B virus multiplication and is effective in both the mouse and chick embryo as well as in tissue culture[15] (cf. Table I). This fact is of considerable importance, for many substances which have shown inhibitory activity in tissue culture or even in the intact chick embryo have failed to show similar effects in mammalian hosts. Like the trichloro derivative, the dichloro compound, DRB, also inhibits mumps virus reproduction in the chick embryo[16] (cf. Table II).

In inhibitory amounts DRB causes no significant toxic effects.[15] It does not reduce the oxygen consumption of host tissue and does not affect the growth of host cells in tissue culture. On withdrawal of the substance, the inhibitory effect on virus multiplication persisted for more than thirty hours. Of perhaps most importance is the finding that this synthetic compound acts after the virus has entered cells and impedes its reproduction inside the infected cells.[17] As a result, the number of new virus particles produced is greatly diminished even though the cells are not demonstrably damaged. Like certain other compounds that are capable of inhibiting the multiplication of some viruses inside infected cells, this substance has no effect upon influenza viruses when they are outside of cells and consequently are not multiplying. The chlorine substituted ribosides of benzimidazole, as they are called, do

TABLE III—INHIBITION OF PNEUMONIA VIRUS OF MICE AND MUMPS VIRUS MULTIPLICATION BY POLYSACCHARIDES

Polysaccharide		*Virus***	*Host*	*Virus Multiplication*
	Mg.			*Per cent of Control*
KPB*	0.1	PVM	Mouse	1
KPB*	0.1	IAV	Mouse	63
KPB*	0.1	IBV	Mouse	100
KPB	1.0	Mumps	Chick embryo	1
KPB	1.0	IAV	Chick embryo	100
KPB	1.0	IBV	Chick embryo	71

* KPB = *K. pneumoniae*, type B, capsular polysaccharide.
** PVM = Pneumonia virus of mice.
IAV = Influenza A virus.
IBV = Influenza B virus.
Data from Horsfall and McCarty[4] in *J. exp. Med. 85*:623, 1947; and Ginsberg et al.[18] in *J. exp. Med. 87*:385, 1948.

not inactivate or destroy influenza viruses. Their action appears to be confined to an effect on the intracellular reproductive process.[15-17]

As was indicated earlier, virus disease does not develop unless virus multiplication occurs. If reproduction of the agent is an essential preliminary to the production of disease, then restriction of the reproductive process should modify the illness. This hypothesis was tested in experiments with a natural respiratory disease of mice. The virus used is a small one, less than half the size of influenza and not quite twice the size of poliomyelitis. The agent causes a uniformly fatal pneumonia in mice. Multiplication of the virus is inhibited by a few micrograms of some bacterial polysaccharides.[4] The most active inhibitors, oddly enough, are the capsular polysaccharides of Klebsiella pneumoniae. Although the polysaccharide from each type of K. pneumoniae inhibits the reproduction of pneumonia virus of mice, designated PVM, and mumps virus, none of them is capable of retarding the multiplication of influenza viruses either in the mouse or in the chick embryo[4,10,18] (cf. Table III).

These findings raise the possibility that a number of different chemotherapeutic substances may be needed if different virus diseases are eventually to be treated effectively.[19] This situation would not be

TABLE IV—CHEMOTHERAPY OF DISEASE CAUSED BY PNEUMONIA VIRUS OF MICE

Polysaccharide		*Treatment given*	*Virus multiplication*	*Extent of pneumonia*	*Died*
	Mg.	*Day*	*Per cent of Control*	*Per cent of Control*	*Per cent*
KPB*	0.02	2	4	43	0
"	0.02	3	12	55	34
None	—	—	100	100	100

* KPB = *K. pneumoniae*, type B, capsular polysaccharide.
Data from Ginsberg and Horsfall[5] in *J. exp. Med. 93*:161, 1951.

greatly different from the current status of chemotherapy in bacterial infections. As is well known, different bacterial diseases frequently require different chemotherapeutic compounds.

The K. pneumoniae polysaccharides affect the multiplication of the small virus, PVM, in a manner closely similar to that of the benzimidazole chloro-ribosides on influenza virus reproduction. They do not affect the virus when it is outside cells.[4] They markedly inhibit intracellular reproduction even when given after the virus has entered the lung cells.[5] The number of new virus particles produced is greatly decreased as a result.

In direct tests of chemotherapeutic effectiveness it was found that the polysaccharide modified the course of the disease and converted a virus infection, which is rapidly fatal in control animals, into a mild illness from which treated animals recovered.[5] This result was secured with a total dose of 20 micrograms of K. pneumoniae polysaccharide per mouse when treatment was commenced two or three days after infection. Before the substance was given, considerable virus reproduction had occurred and definite pneumonia was already present. After the administration of the polysaccharide, further multiplication of the virus was inhibited and soon ceased entirely. At the same time the progress of the pneumonia was retarded and the lesions finally resolved (cf. Table IV).

This is not the only example of what appears to be a successful result in the chemotherapy of infections caused by small viruses. It has been reported[19] that the antimalarial drug, atebrin, both inhibits the

multiplication of equine encephalomyelitis virus and modifies the disease produced by this agent in mice. Other acridine compounds have been found to inhibit the multiplication of mumps and influenza viruses both in tissue culture and the chick embryo.[20,21] In this case also the evidence supports the idea that intracellular reproduction of the viruses was affected.

Various analogues of amino acids, particularly methionine, have been shown to inhibit the multiplication of influenza or poliomyelitis virus in tissue culture.[22,23] These compounds do not inactivate extracellular virus, and are thought to interfere with the intracellular synthesis of new virus particles. The inhibitory effects of certain of these analogues can be blocked by the natural amino acids. This is considered as evidence that these amino acids are involved in the biosynthesis of the virus inside infected cells.[22,23]

Some amino sulfonic acids, which may be thought of as analogues of natural amino acids, also possess inhibitory activity. Such compounds have been found to inhibit the reproduction of influenza virus in tissue culture, chick embryos and mice.[24,25]

Extensive studies on the effects of various compounds on vaccinia virus infection have revealed a number of substances which have inhibitory effects.[26,27] Among the more interesting are certain substituted thiouracils, which are analogues of nucleic acid constituents. Such compounds do not inactivate extracellular virus particles but have a beneficial effect upon the virus disease in mice. The mortality rate is reduced, and treated animals produce less virus than controls.[28]

In addition to the K. pneumoniae polysaccharides,[4,5,18] there are other biological products of uncertain chemical structure which possess inhibitory activity. A mold product, designated Helenine, has been demonstrated to exert a favorable therapeutic effect in mice infected with swine influenza virus or certain encephalitis viruses.[29,30] Moreover, another mold filtrate, designated M-8450, has been found to be active against infections caused by some encephalitis viruses and poliomyelitis virus in mice.[31,32] It may be of considerable interest that although large amounts of the crude filtrate were needed, this material had a beneficial effect on Type I poliomyelitis in monkeys.[33] The incubation period was increased and the incidence of paralysis in treated animals was decreased.

These selected examples represent only a small fraction of the total number of reports that have appeared on the results of chemotherapeutic

experiments on virus infections in laboratory animals. They were selected to indicate current areas of activity in this field and to illustrate the ways in which the problem is being approached. The results that have been obtained thus far provide support for the idea that a substance which inhibits virus multiplication can produce a beneficial therapeutic effect on a virus disease. If further work brings additional support for this concept there will be some basis for an optimistic attitude toward the problem. It is already clear that there is need for much caution and for critical appraisal of results in this field. As events draw nearer to the eventual trial of some inhibitory compounds in the treatment of patients with virus diseases, the reasons for a very careful approach will greatly increase.

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THE TRAINING OF AN OPHTHALMOLOGIST*

The Charles H. May Memorial Lecture

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It is a high honor to give the annual lecture which commemorates the name of one of the great figures of American Ophthalmology. It is also a singular personal pleasure because Charles H. May was a leader in ophthalmology when I first entered this specialty and was one of those whose forms and thoughts influenced my own life.

Dr. May was born in my home city of Baltimore in 1861, and died in 1943 at the age of 82. He was one of a group of distinguished ophthalmologists which included Drs. de Schweinitz, Bull, Weeks, Reese, Casey Wood, Wilmer, Harry Friedenwald, my own father Hiram Woods, and other great men. These men lived and labored in what I like to call the "formative period" of American ophthalmology. They devoted their lives to the intensive study of their specialty, and they placed ophthalmology on a firm clinical base. They built, each in his own individual fashion, the very foundations on which modern American ophthalmology now rests. They are the great figures of their day; and in thinking of their lives and accomplishments, I cannot help but recall Dr. Patton's classic phrase, and wonder if we today are not pygmies perched on the shoulders of those giants of yesterday.

The century and a half preceding this formative period had witnessed the gradual emergence of ophthalmology as a distinct specialty. It had been marked by great advances in ophthalmic surgery, by the recognition of many clinical entities, and above all, by the invention of the ophthalmoscope. The era of Dr. May was marked by the development of refinements of surgical technique, by the intense objective study of ocular semeiology, by the cataloguing and system-

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atic classification of ocular inflammations, degenerations, and diseases, and by the beginning of the study of the pathogenesis of ocular disease. This was the era which saw the introduction of local anesthesia and surgical asepsis, the beginning and the flowering of modern bacteriology, which witnessed the recognition of hypersensitive reactions, and the beginnings of the science of immunology. It was the task of Dr. May and his contemporaries to harmonize their clinical observations with these advances and discoveries; to arrange and classify them in the light of developing ideas of pathogenesis, and so to instruct the oncoming generation of ophthalmologists. They were first students and then teachers. How well Dr. May contributed to this task is well exemplified by his book. First published in 1900, its thoroughness and clarity were immediately recognized. But had Dr. May stopped there, this book would soon have been forgotten. He did not stop. Year after year he revised the text and illustrations in the light of newly acquired knowledge. The eighteenth edition, appearing only shortly before his death in 1943, is still a recognized, authoritative manual for students.

I believe the topic of this evening's lecture—"The Training of an Ophthalmologist"—would have deeply interested Dr. May. It would have interested him because he witnessed and had a part in the early development of the present system of specialized training.

Medical education in 1880 when Dr. May graduated, and indeed until close to the turn of the century, according to our modern standards, left much to be desired. The newly graduated physician had little except his recently conferred M.D. degree to qualify him to treat patients. His future training was in a general hospital, where teaching residency services had not yet been developed, and were often inadequately supervised. In these hospitals he learned what he could of the art of medicine from his superiors and from his own experience. At the completion of this internship he was ready to embark on his specialty training. In ophthalmology various avenues were open to him.

One of the best and most highly esteemed procedures was a course of study in one of the German or Austrian medical centers, where ophthalmology was more highly developed and instruction better organized than in America. This, however, was an expensive procedure and available only to a few. Another avenue was a residency in one of the American ophthalmic hospitals, where unfortunately the resi-

dency training was not yet well organized and left much to be desired. A third conventional avenue was the straight preceptorship system. Here the would-be-specialist became a pupil of an already established ophthalmologist. Under his guidance he worked in the out-patient department of the special eye hospitals and sometimes as the assistant of his preceptor in his operations and private practice. After an indefinite period of such preceptor training, he could enter independent practice. A fourth alternative was to take a so-called intensive course in ophthalmology in one of the "diploma mills." There were several such courses offered in America, sometimes connected with institutions of supposed learning. In these "schools", for the cash payment of several hundred dollars, the neophyte was subjected to a course of didactic and clinical instruction in ophthalmology for a period which varied from three weeks to a few months. At the completion of this course, the student was presented with an engraved certificate which testified to the fact he was now a graduate ophthalmologist, and was turned loose on an unprotected and long-suffering public.

All of these methods of training were open to criticism. The great weakness of the special eye hospitals was the divorce of ophthalmology from general medicine. Even though there were affiliations with general hospitals and a consultation service which on paper appeared splendid, in actual practice these were usually woefully deficient. The straight preceptorship might well be, and often was, excellent. Its success depended on the interest of the preceptor and on his willingness and ability to instruct. The diploma-mill graduate schools were so frightfully bad that they finally brought about their own destruction.

After the turn of the century the pattern began to change. After the Carnegie report in 1910, medical education underwent a drastic reform. The day of the two and three year medical schools was over. Entrance requirements were raised and in some schools a bachelor's degree was required. The medical curriculum was lengthened to a standard of four years' instruction and was reorganized. The residency system was gradually installed in the teaching hospitals, and graduate training in medicine, surgery, and many specialties was organized on a progressive system, usually over a two to four year period or even longer. Ophthalmology kept pace with these advances.

The American Board of Ophthalmology was organized in 1916, the first of the specialty boards for the accreditation of specialists. It

was organized in an effort to elevate the standards of ophthalmology and improve the training of ophthalmologists. My father, Hiram Woods, and my preceptor, George E. de Schweinitz, were among the founders and original members of the Board, and through them I was acquainted with its early history. While I have criticized some of the actions and policies of the Board, nevertheless I believe that, by-and-large, the American Board of Ophthalmology has done a superb job, and that it can rightly claim a goodly share of the credit for the improvement in the training of ophthalmologists, and the consequent elevation of our specialty.

The changes in medical education, the introduction and spread of residency training programs, and the standards set by the American Board of Ophthalmology had an immediate effect on the special ophthalmic hospitals and on the training of ophthalmologists. Some of the isolated ophthalmic hospitals became integral parts of the large teaching hospitals. Others maintained a quasi-independent status, but sought stronger ties with teaching institutions and reorganized their ancillary and residency services. A few of the hospitals, and all the diploma mills, quietly went out of existence. Several recognized institutions of learning now began to offer graduate courses in the basic sciences as they related to ophthalmology. These courses were designed to be taken before beginning a residency training in a special ophthalmic hospital or under a preceptor. The training of an ophthalmologist now began to assume a fairly uniform pattern. While the preceptorship survived, it could now be coupled with organized instruction. It is to the great teachers and leaders of yesterday, men who realized the woeful defects of the old system, that we owe these great advances. While these men respected tradition and treasured the information and knowledge gathered in days gone by, they did not cling to out-moded concepts, or close their minds to the advances of science and education, and refuse to adapt their teaching precepts to these advances.

The three major problems which today confront the Director of a training program in ophthalmology are the selection of personnel, instruction in the basic sciences, and the organization of the clinical service to the end it shall be of the highest possible value to the resident staff who are receiving their training.

The selection of personnel to be trained is all-important, for no man can build a good house out of poor timber. In this selection the

Director of a training program must take cognizance of the requirements of the American Board of Ophthalmology which specify certain prerequisites and general requirements which must be met by all candidates for certification. The prerequisites may be summarized as follows: 1) High ethical and professional standards. 2) Citizenship in the country where the candidate practices. 3) A degree from an approved medical school of high standard. 4) Completion of an internship of not less than one year in a hospital approved by the Council on Medical Education and Hospitals of the American Medical Association. 5) Three years of formalized training plus one year of practice, *or* four years of formalized training, or five years of less formalized training.

Effective January 1, 1957, licensure in the state, province or country where the candidate resides is specified. It is not clear whether this is in addition to the required year's approved internship or supersedes it. In any event, it is of little importance in view of the recent ruling of the Council on Medical Education and Hospitals.

The value of the required preliminary internship has for some time been a question of debate and considerable difference of opinion. On the one hand, no intelligent medical educator could possibly deny that a broad graduate training in medicine, surgery, and pathology widens the horizon of the future ophthalmologist and makes him a better man. In theory this requirement is excellent. In practice, there is considerable reason to believe that this prerequisite does not work for the advancement of ophthalmology, but to its detriment. The reasons for this belief are as follows.

First, a number of excellent medical students become interested in ophthalmology during their undergraduate medical years and decide to make it their life work. Confronted with the requirement of a year's preliminary approved internship, these students applied for approved services in the leading teaching hospitals, frequently in those connected with the institution where they graduated. Being top-flight students they obtained these choice internships under distinguished chiefs. But these distinguished chiefs, keenly on the lookout for the best material, were loath to surrender their prize interns to ophthalmology when the end of the intern year was reached. They therefore offered these excellent interns an appointment in the higher echelons of their services. The intended ophthalmologist, in the most formative year of his life,

interested in his work, influenced by the famous physician under whom he was serving, with an offer before him which almost assured his future, could not refuse. He was weaned away from his first love and lost to ophthalmology. The cream of the crop was culled in this preliminary intern year. The cast-offs were left for the specialties!

Second, the value of the usual rotating service to the future ophthalmologist was seriously questioned. In the successive quarters of medicine, surgery, obstetrics, and the specialties, the intern was under the guidance of chiefs who, while undoubtedly able internists and surgeons, were also usually woefully ignorant of the special medical and surgical problems which would later confront the ophthalmologist. The future specialist therefore did not receive the training best suited to his needs. Too often the rotating internship was a wasted year; often little more than a repetition of the fourth year of the medical school and under the guidance of Chiefs-of-Service who were under no obligation to teach.

As a result of these two factors, the Chiefs of the ophthalmology services in both the teaching and the special ophthalmic hospitals found themselves plagued by the continued seduction of their brightest prospects during their required preliminary intern year, and distressed by the inadequately trained material arriving from the rotating services. To obtain better material to train, they turned to the newly graduating classes. Here they encountered the difficulty of the American Board's requirement of an approved preliminary internship. But this difficulty was not insurmountable for the teaching hospitals.

Prior to 1953, the Council on Medical Education and Hospitals of the American Medical Association had limited their approval of straight internships to medicine, surgery, pediatrics, and pathology. However, in certain teaching hospitals, with well developed services in the various specialties, the Council had included these "unclassified" specialty internships in the general approval given the hospital. When the Intern Matching Program was established, medical students applying for these unclassified specialty internships were admitted to this program, and successful applicants were duly assigned to the straight specialty internships. This met the full requirements of the American Board and of the state licensing boards, which required an approved internship for licensure and allowed the graduating student to embark immediately on his specialty training. Under this arrangement, the ophthalmology

service of a teaching hospital could compete with other services in the quest for the best material. This scheme worked, and worked well. I can truthfully say that during the twenty-odd years I have been charged with training ophthalmologists, by-and-large, the best men I have had and those who have made the greatest successes of their later lives, have been the top-flight medical students who began their training directly after graduation without a preliminary internship elsewhere. However, in 1953, this well-working scheme was suddenly interrupted.

On July 30, 1953, without previous warning of any kind, and without consultation with ophthalmologists or with the American Board of Ophthalmology, the Council on Medical Education and Hospitals suddenly withdrew their previous indirect approval of these straight specialty internships offered by the teaching hospitals, and now limited their approval specifically to straight internships in the medical, surgical, and pediatric services, and to rotating internships. Later, for one further year only, the Council gave approval to straight internships in pathology and obstetrics. The first year's training in the other specialties was now classified by the Council as "assistant residencies." The reason for this sudden action is not clear. The Secretary of the Council states that this reclassification of the first year of specialty training is in no way a reflection on the excellence of the service, but is merely one of semantics. Whatever may have been their reason, the effect of this ruling was instantaneous. Almost without exception, men who were to graduate in 1954 and who had previously planned to embark directly on their training in ophthalmology, either did not apply or withdrew their applications. As far as I have been able to learn, there was only one such application from a 1954 graduate, and none have been received from the men to graduate in 1955.

The present policies of the Armed Forces for the procurement of medical personnel further complicate the picture. Under this policy physically qualified physicians are liable for military service after one year's internship. Men completing a general internship are reluctant to begin their specialty training when it will in all likelihood be interrupted by compulsory military service. Recently, under the direction of Dr. Berry, the new Assistant Secretary of Defense, there has been instituted a program whereby some men may have their military service deferred in order to obtain training in the specialties. How this will

work out remains to be seen. Since only 300 applicants, distributed among fifteen specialties, were deferred this current year, it would appear this will have little immediate effect. Nevertheless, it is obvious that as the older group of qualified ophthalmologists complete their military service, the Armed Forces will have an acute need for young, properly trained specialists. If they have the foresight to realize this, and defer a sufficient number for specialty training to satisfy their future needs, the result will be beneficial not only for themselves, but for the future of American medicine.

Thus the recent action of the Council on Medical Education and Hospitals and, to a less extent, the policies of the Armed Forces relative to medical personnel, have curtailed the flow of the best material to ophthalmology. The applicants are now largely limited to men who have completed an internship elsewhere and are physically disqualified for military service, to women who have completed an internship, to older men who have become dissatisfied with general practice and wish to specialize, and to veterans who have completed their military service. By far the best of these are the veterans. These men usually have a well-defined purpose, a keen desire to make the most of their G.I. benefits, and in the main are excellent candidates for training.

In the final selection of men to be trained, I believe the best yardsticks to estimate their potential abilities and future success are an evaluation of their record in medical school, the unbiased opinions of their Deans and former instructors, their record after graduation, and the information to be gleaned from a personal interview. In this interview the personality of the applicant can be assessed, his background and his earnestness of purpose evaluated, his ambitions and desires in medicine revealed, his primary interest in an academic career or as a practitioner determined, and any originality or interest in investigation searched for. It is on these points that I believe the final selection should be made.

The second point to be considered in the training of an ophthalmologist is the instruction in the so-called basic sciences. While the future specialist has received instruction in these subjects during his undergraduate medical years, this instruction was not specifically concerned with its relation to ophthalmology, and moreover, it was imparted to the student some four years or more previously and much of it has been forgotten.

The American Board of Ophthalmology makes a specific requirement for instruction in these basic sciences as they relate to ophthalmology. The necessity of this requirement can scarcely be questioned. It cannot be left to chance that the future ophthalmologist will pick up and assimilate this fundamental knowledge during his clinical training. Instruction in these basic sciences must be formalized and systematized. Competent teachers in each subject must be obtained and proper facilities for such instruction must be provided. The questions are:—What should be the pattern of the instruction? How far should it be carried? When should it be given?

The objectives of teaching in the basic sciences are to instruct the future ophthalmologist in the fundamentals of the various disciplines as they relate to ophthalmology and to acquaint him with the new developments and special techniques which may be applicable to the problems of his specialty—in short to satisfy the needs of the future clinician and stimulate the hunger of the future investigator.

Should the instruction in the various subjects be didactic, be through actual laboratory experience, or be a combination of both? There is no immediate, practical, satisfactory answer. Certainly it is difficult to make out any case for pure didactic instruction. Admittedly, there is no substitute for actual laboratory experience—what Dr. Friedenwald has aptly called "learning through doing." But if the future ophthalmologist is to acquire his knowledge of the basic sciences through adequate laboratory training in each branch, the way is long and arduous. It would require years, and not months. The practical answer therefore appears to be a compromise—actual laboratory experience and personal instruction in the basic sciences which are most closely related to clinical ophthalmology and exposure to the laboratory procedures of the more remotely connected sciences, rather than actual experience in them. The question of the proper balance between laboratory experience and didactic instruction has been fairly well resolved for pathology and bacteriology, and here the student may master not only the fundamentals of ophthalmic pathology and bacteriology, but also the newer developments and special techniques through a properly designed laboratory course under a competent instructor. In anatomy it is more difficult, but a combination of actual work in the dissecting room, study and personal instruction in the stereo-anatomy of the orbit, and the histology of the eye ball will give the student the proper foundation

for his clinical work. In physiological optics, laboratory experience with the optics bench, didactic instruction in physical optics, and actual work with patients round out the program. In physiological chemistry, organ physiology, and physics, the very magnitude and complexity of these subjects make it difficult, if not impossible, to design a laboratory course within the practical limits of available time. Recourse must be had to didactic teaching and laboratory demonstrations in which the student can often participate. In these exercises such special procedures as the injection technique now so much used in anatomy, the use of isotopes, cathode-ray oscillography, histo-chemical and micro-titration techniques can be demonstrated. The student, in the time available to him, cannot be expected to become a master of these techniques, it is sufficient if he is acquainted with them and with their potentialities in his specialty. If properly exposed, he may well catch fire and explore these distant vistas on his own initiative.

In designing the overall pattern of instruction in the basic sciences, there is one danger which must be avoided. This is that some individual instructor, in his enthusiasm for his subject, may carry the extent of his teaching far beyond the bounds necessary for the training of the average clinical ophthalmologist, and thus throw the entire program out of balance. It is therefore the duty and obligation of the Director of the department to see that the instruction in the basic sciences is not only adequate, but at the same time kept within proper limits. He must be cognizant of the content of the various courses, see that they are amplified or curtailed as may be necessary, and that they dovetail with each other to make a harmonious whole.

Should this basic instruction be given before the clinical training, or synchronous with it? If the clinical training center is so situated it cannot command proper teachers or provide the necessary facilities, then of necessity these basic courses must be divorced from the clinical training and be given independently. This is then the function of the excellent courses now offered by some of our leading universities. However, if the clinical training center is so located that it can command teachers and provide facilities, I believe the instruction in the basic sciences should be given synchronous with the clinical training. It makes a far more lasting impression on the student if he is taught the bacteriology of conjunctivitis and the sensitivity of pathogenic organisms to antibiotics while he is treating infected eyes, than when such

instruction is imparted solely by didactic lectures and laboratory exercises. Similarly, he will better appreciate the importance of physiological optics when he is learning retinoscopy and practical refraction. Such examples can be multiplied endlessly.

The third point concerns clinical instruction. The American Board requires either three years' formal training in a residency followed by one further year of practice or institutional work, or five years of less formalized training and practice in ophthalmology. Let us first consider the less formal approaches.

The most important of these is a preceptorship under an already accredited ophthalmologist. This must now be supplemented by a preliminary or concurrent course in the basic sciences and the training must extend over a minimum period of five years. Since the special ophthalmic hospitals and the ophthalmological services of the teaching hospitals together can scarcely train sufficient men to compensate for the annual death rate among ophthalmologists, let alone care for the needs of an increasing population, it is evident that for a considerable length of time the preceptorship type of training must continue.

Training through close association with an established ophthalmologist may in some respects be remarkaby good, but now it can never be adequate. Ophthalmology has grown greatly in the last four decades, and is now a many-faceted diamond. While it is commonly classed as a surgical specialty, surgery is only a very small proportion of the average ophthalmologist's practice. Ophthalmology today invades internal medicine, physiological and histo-chemistry, bacteriology and immunology, neuro-physiology, physiological optics, and other disciplines of science. The preceptorship training is inadequate for the simple reason it is impossible for any preceptor, never mind how brilliant and distinguished he may be, to encompass fully all these myriad fields and properly to expose his pupil to all the vistas of these disciplines, in any one of which the budding ophthalmologist may find the expression of his own individuality. He can fashion his pupil in his own mould, and the trainee may develop into either a brilliant reflection or a poor reproduction of his teacher. Tudor-Thomas expressed much this same thought when he wrote: "The days of the old clinician are gone, when a man could be dependent solely on his own observations in the full treatment of a patient, whatever the condition may be."

Another informal approach to fulfillment of the clinical training is

through fellowships of various kinds or through the traineeships recently established by the National Institutes of Health. These fellowships and traineeships usually pay a stipend sufficiently large to cover living expenses. They are usually designed to provide facilities for research work and advanced training, and as a rule afford little opportunity for personal surgical experience, the available surgical material on most ophthalmic services being reserved for the resident staff. However, the fellow or trainee primarily interested in research, but who desires ultimate accreditation in ophthalmology, can supplement his investigations with clinical work over a five year or longer period until he has acquired sufficient clinical experience to apply to the Board for examination. It is obvious that these approaches are applicable only to a few selected individuals.

The formal training required by the Board can be obtained by a residency either in a special ophthalmic hospital or on the ophthalmological service of one of the general teaching hospitals. The only stipulation made is that the training, including time devoted to the study of the basic sciences, extend over a minimum period of three years. Thereafter the candidate must have one year's further experience in practice or institutional work. The pattern of the clinical instruction is not dictated by the Board, but is left entirely to the discretion of the institution offering the residency. This immediately brings up the first question: Which type of service—the special ophthalmic hospital or the ophthalmological service of the general teaching hospital—provides the best training for the future specialist?

I have had little experience with ophthalmic hospitals which are separate from general hospitals. I speak, therefore, from the limited and probably biased viewpoint of a Director of the Department of Ophthalmology in a teaching hospital. Nevertheless, let me explore the question of the relative merits of training. Obviously, the answer to this question depends on the individual excellence and facilities offered by the different institutions. However, if the ophthalmological service in the teaching hospital is sufficiently large and is properly organized, I believe it is the superior of the two. I say this with the greatest respect for what the special ophthalmic hospitals have done and are still doing. One has only to look at Moorfields in London, at its contributions and accomplishments in over a century, to realize the stature such institutions can attain and the training they can provide. But I believe even Moor-

fields would have gone much farther and accomplished more, had it been an integral part of a large university teaching hospital. Ancillary and consulting services can be arranged in a special hospital, but what the trainee will lack is the day-by-day and hour-by-hour contact with other services and disciplines which border and impinge on his own field. It is of unparalleled value to the ophthalmic resident to be called from his bed at night to see a patient admitted to the accident ward with a cavernous sinus thrombosis and to aid in the differential diagnosis, to advise on the orbital cellulitis of a child with infection of the accessory nasal sinuses, to accompany his fellow interns in medicine to the medical wards and examine the fundus lesions of patients with systemic disease. And above all, the ability to enlist immediately the interest and aid of his fellow residents on the other services—medicine, pediatrics, neurosurgery, etc.—in the problems of the patients on his own ophthalmic wards is of the highest educational value. No number of visiting consultants, prearranged clinics in ancillary branches, didactic teaching, or what not, can compensate for the loss of this continual personal contact with other services. This is being realized more and more and as a result many distinguished ophthalmic hospitals have amalgamated with general hospitals, where physically as well as spiritually, they become an integral part of the great mosaic of modern medicine.

The manner in which an ophthalmological service should be organized to the end that it provides the best possible care for the patient and at the same time is of maximum value for the training of the house staff, will depend on the facilities available and will vary greatly in different institutions. The value of the graduated residency system is now so generally recognized that it needs no special plea for its adoption. On the question of clinical instruction, the organization of the service, the duties and obligations of the Chief-of-Service and his senior associates, there will be many different opinions. I can only express my personal ideas.

In the first year, regardless of previous experience, the trainee should be assigned to what is commonly called "intern duty." He should be required to take a careful history and make a complete physical examination on every in-patient. He should be responsible for having all routine blood and urine examinations done on every patient—whether he does them himself or sends the specimens to a central laboratory. He should make a complete ophthalmological examination,

and record his findings and opinion. In these duties he should be supervised and, when necessary, helped by his seniors on the resident staff. Thus he learns to appreciate the significance of the patient's medical background and its relation to the specific ophthalmic problem. He should present his patients to the senior resident, to be criticized for mistakes and omissions, and helped in difficulties. Thereafter his training becomes the duty of the Chief-of-Service.

There are certain cardinal precepts the Chief-of-Service should always carry in mind. First of all, the tempo of his service should not be designed for the mediocre man. Not all men can be brilliant, but as Alan Gregg well expressed it, nipping at the heels of laggards is not the essence of leadership. The service should be designed to give full scope for the development of the intelligent and inquisitive mind. The plodder should be exposed to all the service has to offer and be encouraged to avail himself thereof, but the tempo of instruction should not be set at his level. Second, the Chief-of-Service must accurately evaluate his own abilities and limitations. Like the preceptor, he cannot cover all fields of ophthalmology. He must select his staff, part-time or full-time, with the idea of compensating for his own deficiencies, and with a realization of the special knowledge and qualities each member of the teaching staff can offer. Thus one of his senior staff is selected for his superlative operative technique, another for his knowledge of ophthalmic neurology, another for his originality of mind and his proven research ability; others for their special interest in such subjects as retinal separation, myology, glaucoma, immunology, bacteriology, chemistry, ophthalmic pharmacology, and so forth. The staff should not be selected on the basis of a successful private practice, on personality, or on the old school tie. Rather should they be selected, appointed and promoted for special qualities they may possess and for what they can individually contribute to the training program. It is the duty of the Chief-of-Service to see that all fields are covered as well as possible, regardless of his own interest or lack of interest in any special subject. If men qualified to cover some particular field are not available, they should be sought for and brought in from outside. Within reason and with regard to the overall program each staff member should be given adequate facilities for the practice, investigation, and instruction of his special discipline. This will often result in the development of special clinics or subdepartments, but no one discipline should be allowed to dominate the

field at the expense of others. It is the duty of the Chief-of-Service to weld these various clinics or sub-departments into a harmonious whole. Each trainee, through his years as intern, junior and senior assistant resident, should be rotated through the special sub-departments and exposed to each. Thus he becomes a well-rounded man, who well may develop an independent interest in some particular field in which he will do special work and often original investigation.

It is the duty of the Chief-of-Service to assume the major burden of the routine clinical instruction. It is a duty he cannot escape however tiresome and repetitious it may be. It can only rarely be assigned. Only by such continual clinical teaching and contact with his resident staff, can he really know the individual members, realize their faults and weaknesses, which he must endeavor to correct, and their interests and brilliance, which he must similarly endeavor to advance and to exploit.

How should such clinical instruction best be given? I have already elsewhere expressed my opinion on this subject. It is my opinion that the essence of clinical teaching is bedside instruction, using the ceaseless flow of widely different clinical material on the wards, making ward-rounds with the entire staff, studying and discussing each case, the symptomatology and possible therapeutic procedures which may be employed, and following the progress of the patient to recovery or to disaster. That there will be endless repetition is inevitable, but this is fortunate, for gradually the basic principles and the pitfalls of diagnosis and therapy are learned by the trainee and he finally wins through to the acquisition of independent judgment.

There is a technique in the conduct of ward rounds which I believe is important. After the case has been presented by the senior resident and examined by the Chief-of-Service, the intern to whom the patient was originally assigned should be the first one asked to discuss the case and express his opinion. Thereafter the opinions of the other interns in order of seniority, and those of the assistant residents should be asked. The members of the visiting staff who may be in attendance should thereafter be invited to make comments or suggestions. Finally, in the light of the presentation, the examination, the discussion by the junior and senior men, the Chief-of-Service should sum up the case, express his opinion and outline the therapy to be followed. Often the Chief may be mistaken in his summary. If so, it will usually become apparent as the patient is followed throughout his stay in the hospital. It is in-

contestable that the staff will learn as much and more from the well-considered mistakes of the Chief-of-Service as they will from an accurate and spectacular diagnosis.

Such staff ward rounds offer unending opportunities for teaching. New developments in ophthalmology, especially as related to an individual patient, can be reviewed, evaluated and discussed. Many cases will reveal the huge vistas of our ignorance and will make apparent many of the unsolved problems of ophthalmology. These can be discussed, possible methods of approach and solution pointed out, and frequently such exposition of ignorance and crystallization of problems will fall on fertile soil. The Chief-of-Service will then be rewarded for his toil by exciting the interest of his pupil, and have the satisfaction of guiding him into original investigation. Such investigations may or may not be fruitful – the important thing is that interest has been awakened and the seeds of scientific curiosity implanted. From such beginnings worth while investigations grow.

The importance of the Chief-of-Service stimulating research and independent investigation cannot be over-emphasized. He may have on his university staff men who are much more original and far more distinguished investigators than he is himself. But the young trainee knows little or nothing of the unsolved problems of ophthalmology or the means by which they may be attacked. He is primarily interested in clinical ophthalmology and he looks to his Chief-of-Service for guidance. If he does not find in this Chief an interest in research and investigation, his own interests are liable to remain wholly clinical, and he is prone to regard the distinguished investigators in the adjacent laboratories as queer individuals who spend their time pursuing their own fantastic notions. But if he does find in his Chief an enlightened interest in research, if the problems which beset the ophthalmologist are exposed to him, if the methods by which they may be attacked are discussed, and especially if this is done as part of his clinical instruction, a latent spark of curiosity within him may suddenly be fanned into flame. He will see the investigator in a new light, not as a person there primarily for the purpose of occasionally being of aid to the clinician, but as an individual with a real purpose. If encouraged, the young trainee will seek out the laboratory worker, will often become a participant in an already organized research problem, and will enlist the aid of the trained investigator in the formulation of his own problem. Not all men

have in them the germs of scientific curiosity, but all men should be exposed to the idea of research. A few who are blessed with a divine discontent for accepted dogma and an awareness of the existing problems, may venture into the unknown and there occasionally find treasure.

Training in ophthalmic surgery requires special mention. Such training may aptly be divided into instruction in surgical technique and the acquisition of surgical judgment. The first presents little difficulty. The neophyte is eager to learn, and as he becomes proficient, he is rewarded by the joy of individual personal accomplishment. Surgical technique must be taught in the operating theatre. The budding ophthalmologist should be given a few months' preliminary training in the preparation of the patient, in anesthesiology, in the choice of instruments, in the duties of the nurse-in-charge and of the various assistants, all to the end that he may learn the routine of the operating room. Thereafter, serving first as junior assistant to his seniors on the resident staff, first on minor procedures and later on major procedures, he quickly learns the general technique of various ophthalmic operations. When this point is reached, he should be assigned as assistant to the senior staff surgeons on their private cases. Here with sufficient opportunity and personal instruction, the intelligent young assistant resident with good hands can, within the space of a few months, learn the fine minutiae of ophthalmic surgical technique to the degree that he becomes equally skillful as his teacher, and frequently more so. I sincerely believe the actual performance of ophthalmic surgery is preeminently the sphere of the younger man. With steadier hands, unhampered by presbyopia, with the confidence of youth, and with proper training, he is often the technical superior of his older instructor. When he has mastered the technique and learned how to meet and to avoid complications, he should be allowed gradually to embark on his own independent surgical career. But for a considerable length of time this should be under the restraint and guidance of the senior house surgeon.

In this supervised, semi-independent surgical career, the budding surgeon must be given the maximum opportunity to gather experience and to develop his individual technique. To this end he must have operative material. To provide such material, it is imperative that the surgical patients on the public wards be reserved for actual operation by the resident staff. Only with the greatest rarity should the Chief-of-Service operate on ward patients or permit his visiting associates to do

so. If some new technique, with which the resident staff is as yet unacquainted, is involved, or if there are peculiar personal or social factors which make it wiser for the older man to intervene, then of course the Chief-of-Service should exercise his prerogative and operate on ward patients, or permit his senior staff to do so. But with such occasional exceptions, the ward operative work should be reserved for the resident staff. The older men have had their training, they have their own private patients, and they should be glad to step aside and give full opportunity to the younger men. And make no mistake, under such a system, with proper preliminary training and under supervision, the younger men do a superb job and the ward patients get equally good service as do the private patients, if indeed it is not better.

The acquisition of surgical judgment is vastly more difficult. The late and great George E. de Schweinitz once aptly remarked that the best ophthalmic surgeon was the one who knew when not to operate. This is only another way of stating that surgical judgment is vastly more important than surgical technique. Just as surgical technique must be taught in the operating theatre, just so surgical judgment must be taught on ward-rounds at the bedside. This is the duty of the Chief-of-Service. The surgical problem of each operative case, the various procedures available, the ones best suited to meet the individual needs of the patient, the dangers involved in each, what safety precautions can be taken to minimize dangers of operative and postoperative complications – all of these must be considered and discussed, and in the light of this discussion, the final decision for the care of the patient is reached. At the first and subsequent dressings, the situation is reviewed, any mistakes in judgment or technique must be clearly exposed, the possible reasons for any postoperative complications explored, the final result evaluated, and the subsequent care of the patient outlined. Month after month, on every surgical case, the young ophthalmologist should be exposed to such thoughtful analysis and self-examination for any errors of commission or omission. It is an old but true saying that more is learned by the careful study of one's mistakes than by one's successes. It is only by such long and painstaking study and review that sound surgical judgment is finally achieved and the mature surgeon is trained and developed.

There is one remaining phase of a properly organized training program which should be mentioned. This is usually termed "short in-

tensive courses"—a somewhat inappropriate term. I do not believe any experienced teacher would make a case for straight didactic instruction in the sense of reading assignments, reviews, and quizzing. Such methods of teaching may result in the student memorizing certain facts, but it certainly does not teach him to think. Nevertheless, a certain amount of didactic instruction is of value to the extent it enables the trainee to formulate and organize his bedside instruction and so achieve orderly knowledge. This is, I believe, best accomplished by a series of lectures, symposia, seminars – call them what you will – held throughout each academic year. These exercises should be conducted by the staff member best qualified and versed in the individual field, or occasionally by guest lecturers. Such subjects as practical refraction and retinoscopy, the various phases of medical and neuro-ophthalmology, glaucoma, tonography, clinical-pathological correlation, the results of recent and new investigations, should be taken up at individual sessions. The story of the development and present status of each topic, the pathogenesis, clinical symptomatology, pathology and therapeusis of various disease entities, should be systematically reviewed, and each lecture should be followed by a period of questions addressed to the lecturer, and by a general discussion. These are prepared exercises in contrast to the impromptu teaching on ward rounds. These seminars round out and systematize the training program.

One word concerning the duration of such a training program. After three years, if the trainee has had a previous year of general internship, he is ready to take his Specialty Board examinations. If he has not had such a preliminary internship, he must spend an additional year in practice or as a fellow, preferably the latter, before certification. But in any event, after an intensive three years' training he should be ready and safe to venture into independent practice. If this is our only goal in training ophthalmologists the immediate task is finished. But if we wish to develop real investigators and professorial material, much more remains. At the end of three years, an outstanding man should be kept on for at least two additional years' residency training. The first of these years can well be spent as the personal assistant of the Chief-of-Service, where in daily personal contact with the Chief on his private patients, in his research projects, and his administrative problems, he can draw from him the last vestiges of information the Chief has to offer. The final and fifth year should be spent as Resident–

in full charge of the wards and the resident staff, subject only to the direction and discipline of the Chief-of-Service. The Resident should be responsible for the assignment of the resident staff to their various duties, for the allotment of operations to assistant residents, for the decision on any emergencies which may arise. His own operative schedule should be heavy, he should do from a third to one-half of all operations on ward patients, assigning the remainder to his assistants. He will have little time for original investigations of his own, for his job is arduous, time-consuming, and responsible. He can and should turn to his Chief and to the senior staff members for needed help, and such help should always be forthcoming. But in the end he learns to assume responsibility, to make sound decisions, and to stand on his own feet.

At the conclusion of his resident year, with five years of intensive training behind him, and the last year in a position of great responsibility, the Resident no longer needs a guardian. He is ready for independent work, and must now make the decision whether he wishes to devote himself to academic ophthalmology and research, to private practice, or to some difficult compromise between the two. If he decides in favor of an academic life, he is ready for appointment as an assistant professor. In such a position, with a modest stipend, but free from the necessity of practicing to make his living, he can acquire teaching experience, learn departmental administration, and pursue independent original investigations. It is from the small pool of such well trained clinicians, teachers, administrators, and investigators that our professors of ophthalmology and department heads are being recruited.

One last word on the duties and obligations of the Chief-of Service charged with the training of an ophthalmologist. I have outlined his responsibility for the selection of his trainees, for the appointment of his staff, for the need of critical self-evaluation and the assignment of duties to specially qualified men better able to discharge them than he himself can do. I have stressed that he must reserve all possible operative work for the training of his resident staff, and not for himself or his senior associates. I have emphasized that he himself must carry the major portion of the burden of clinical instruction. It is his duty to stimulate and to further research and original investigation. But this is not all. He has still one great duty and obligation.

It is his paramount duty to help his staff over their difficulties, to

encourage the none-too-brilliant man, to meet their individual problems with sympathetic understanding, to remember that he too was once young, impetuous and subject to all the arrogance and uncertainties of youth. He must teach his staff that the patient is a human individual with his own weaknesses, problems and mental blocks; and that these must be considered in his treatment. He must train his staff not only to be ophthalmologists and investigators, but also to be humanitarians. And above all, he must teach them intellectual honesty.

TO THE OFFICERS OF MEDICAL SOCIETIES IN THE METROPOLITAN AREA

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AN EVALUATION OF PRESENT DAY SURGERY FOR MITRAL STENOSIS*

LOUIS A. SOLOFF† AND JACOB ZATUCHNI†

PRESENT day surgery for mitral stenosis at the Episcopal Hospital in Philadelphia was begun in 1948.[1] On first thought, it would appear that sufficient time has now elapsed to permit valid evaluation of this type of therapy. There are, however, many reasons why even seven years is too short a time to assess with finality the beneficial effects of mitral valvotomy in individuals with mitral stenosis. Statistically, it appears idle to attempt even to discuss long term beneficial effects because, compared to the natural history of mitral stenosis, which often outlasts the professional life of a physician, the postoperative intervals are far too short to make such a discussion meaningful.

Even short term beneficial effects of surgery are difficult to evaluate because many of the early reports and, indeed, the vast majority of those today, predicate beneficial effects on improvement in functional capacity of individuals after surgery. No one, of course, questions the importance of functional improvement. Indeed, the major function of a physician treating an ill patient is to restore him as close to normal activity as possible. Without considering potential bias of both physician and patient in interpretation of improvement, reports of this sort imply that individuals with mitral stenosis cannot improve unless mitral valvotomy is done. Yet, every physician knows that rheumatic heart disease with mitral stenosis is a chronic illness that may remain stabilized for years and that this stable state may be upset by events producing symptoms and signs, none of which is necessarily specific for mitral stenosis or its degree, and, indeed, some of which may not even be related in any way to the mitral valve. These exacerbations may be unpredictable in time, duration or frequency. Their causes may be manifold and, in themselves, have variable prognoses. Individuals may die in an exacerbation. More often, depending upon

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their causes and severities, the individual's resistance and his cardiac reserve, disappearance of the phenomena characteristic of the exacerbation may occur either with no detectable change in residual cardiac disease or with an increase, or, indeed, at times, with a decrease in recognizable deviations of the heart from normal. In other words, the functional capacity of the individual may change naturally or following medical treatment; and, this change may be recorded in any type of classification adopted.

At the beginning of the present surgical era, it was to be expected that individuals with the most rapid impairment of cardiac function should most eagerly seek a restoration of health by means of this new technique. Surgeons and cardiologists, buttressed by the irresistible logic of the procedure, were reluctant to refuse such individuals surgery. Physicians were told that it was their responsibility to have individuals with mitral stenosis referred to surgeons. The minds of these sick people were properly prepared by ubiquitous and repetitious propaganda in the lay press. The propagandist had already taught us that individuals rarely can resist repetition. Remissions occurring naturally or induced by medical therapy were regarded as indications for surgery rather than evidence that the contracted mitral orifice was not the immediate cause for the change in cardiac function. The implication was that, regardless of the immediate cause for change in functional capacity of the individual, it was the contracted mitral orifice that made the illness serious. Therefore, adequate surgery would prevent such a train of events in the future.

Although there are considerable physiologic data to support such an hypothesis, as there are pathologic data to indicate that surgery is sometimes inadequate, and at other times ineffective even though adequate, it should have been obvious to all that statements of improvement under such circumstances are not justified unless the basis for comparison is the effect of similar precipitating factors in the future or the functional status of the individual before the onset of his exacerbation. No attempt was made to distinguish acute events that tend more frequently to occur early in the life history of mitral stenosis and are frequently self-limited from those that occur late. On the contrary, individuals were and frequently still are lumped together into specific functional classes regardless of age, of cause and duration of disabilities and their response to non-surgical therapy, of heart size,

of the type of heart failure and of the number and frequency of previous exacerbations. Yet, we all know that each one of these factors is important in evaluating prognosis of both the acute exacerbation and the long term course of the illness. It is because of this tendency to equate individuals with similar functional incapacities regardless of cause, duration or the extent of cardiac disease, that we have been unable to accept as valid most of the reports of the percentages and degrees of even short term improvements attributed to surgery. This statement is not to be interpreted as meaning that we believe that mitral valvotomy has no value.

The problems of the cyclic nature of functional changes in individuals with mitral stenosis are part of the larger subject of the natural history of mitral stenosis as affected by the best available medical therapy. Unfortunately, all studies on this subject are as yet incomplete or inconclusive. As a base line, we may use May Wilson's prediction based on studies before the widespread use of antibiotic therapy.[2] Dr. Wilson stated that the survival rate for individuals with rheumatic heart disease twenty years after onset of their disease was 74.9 per cent. She predicted that 50 per cent would live more than 45 years after the initial occurrence of the disease. United States Government statistics tend to support this statement and indicate that the average age at death for all individuals with rheumatic heart disease in 1951 was fifty-five years.[3] According to Wilson, the over-all death rate was 14.7 per thousand per year and the death rate five to ten years after onset was usually less than 1 per cent per year. This mortality can be compared to that of mitral valvotomy that has a minimal mortality of 4 to 5 per cent even for the individual with asymptomatic mitral stenosis. If Wilson's statistical conclusions are correct, there can be no excuse at this time for subjecting asymptomatic individuals with mitral stenosis to operation.

Actually, prognosis of rheumatic individuals has steadily improved during the past century.[4] It has improved rapidly during the time interval of Wilson's study and improvement has been accelerated by the introduction of antibiotic therapy. Furthermore, the age at death is higher for any succeeding age group than any preceding one or than the group as a whole. Thus, at age thirty-seven years, the average age at operation, Wilson's prediction implies that not 50 per cent but 83.4 per cent will survive the age of fifty. Only 16.6 per cent will

have died below the age of fifty. Strangely, this percentage, 16.6 per cent, represents our surgical group mortality within three years of operation of the first 500 individuals subjected to mitral valvotomy.[5] The average age at death was forty years. If we are to improve on Wilson's statistics, it will be necessary for us to have no more deaths in this group for considerably more than ten years. Unfortunately, deaths have occurred at such a rate after this three year study that we are in a situation similar to Tristram Shandy who found himself each succeeding year, 364 days behind the preceding one.

Such a simplification of statistics is unfair in some ways to medicine and in others to surgery. Obviously, the surgical group is composed almost entirely of individuals with symptoms and the medical group may contain a significant percentage of asymptomatic individuals. On the other hand, Wilson's group includes all individuals with rheumatic heart disease and not just those with isolated or predominant mitral stenosis and no distinction is made of the disability causing death. Clearly, not all disabilities and deaths in individuals with mitral stenosis are potentially preventable by mitral valvotomy.

In order to obtain a more distinct picture of the present day problem of mitral stenosis, we have analyzed all deaths of individuals with rheumatic heart disease from 1945, when antibiotic therapy was first widely used, to the birth of present day surgery for mitral stenosis in our hospitals. The details of this study are published elsewhere.[6]

In essence, there were 141 individuals with rheumatic heart disease who died. This group represents 8.2 per cent of 1718 individuals admitted with a clinical diagnosis of rheumatic heart disease which, in turn, represents 0.9 per cent of 188,066, the total hospital admission.

Deaths were divided into seven clinical categories:

1. Sixteen (11.3 per cent) died of diseases unrelated to rheumatic heart disease or its sequelae.

2. Nineteen (13.5 per cent) died of rheumatic carditis. The average age at death was 20.9 years. These individuals all had florid carditis, the type that even the surgical enthusiast refuses to accept for surgery. Moreover, only two had mitral stenosis and one of these had extensive rheumatic pneumonitis. We have followed one such individual subjected to mitral valvotomy. Although surgery was adequate as shown at autopsy, progressive deterioration of the heart and its function occurred until death fifteen months later at the age of

twenty-one. Yet, until the last few days of her life, the patient, her physician and her surgeon were confident that surgery had been effective.

3. Sixteen (11.3 per cent) died of bacterial endocarditis at an average age of 37.4 years. Only one individual had isolated mitral stenosis. He was fifty-six years old with hypertension and a precordial systolic murmur. He was thought to have aortic stenosis but autopsy showed mitral stenosis with an orifice of 1½ fingers. The left ventricle was 1.75 centimeters thick. There were vegetations on the mitral valve and an embolus in the pulmonary artery.

4. Nine (6.4 per cent) died of pulmonary infarction with heart failure at an average age of 41.1 years. Only one had isolated mitral stenosis, the mitral orifice being rigid and 4 centimeters in circumference. He had thrombosis of the right pulmonary artery with infarction of the right middle and lower lobes of the lung.

5. Thirteen (9.2 per cent) died of systemic embolism with preexisting heart failure at an average age of 47.7 years. Only one had isolated mitral stenosis, a fifty-three year old man admitted into the hospital in coma with hypertension and atrial fibrillation. At autopsy, the mitral orifice was 6 centimeters in circumference.

6. Twelve (8.5 per cent) died of systemic embolism without heart failure at an average age of 46.5 years. All had atrial fibrillation. Of the three with autopsies, all had isolated mitral stenosis.

Here then is the first group in which mitral valvotomy, on theoretical grounds, may do good. The practical difficulty lies in predicting which individuals with mitral stenosis and atrial fibrillation are doomed to die of embolism, or, indeed, sustain any type of embolus. Only 25 per cent of those dying of embolism had sustained a preceding one, the interval varying from one to three years. Furthermore, of those sustaining a major embolus with survival, less than one-half will die of a succeeding embolus.[7] The greatest difficulty, however, is that mitral valvotomy is accompanied by the highest percentage of embolism. The incidence is significantly higher for those with atrial fibrillation, varying in different series from 5 to over 10 per cent. Indeed, it is our commonest cause of operative death. It probably occurs slightly more frequently in those with a history of embolism in the past. The incidence of embolism occurring naturally is about 1 per cent per year.[8] Therefore, there can be no excuse for performing

mitral valvotomy as a prophylactic procedure against embolism. Furthermore, it is commonly stated that once an individual passes the hurdle of operation without embolism, there is very little chance of sustaining one in the future. This statement overlooks the fact that the incidence of embolism at operation is so high that it will take from five to twelve years free of embolism to reduce the incidence of surgically produced embolism to that occurring naturally. It also overlooks the fact that most operations are done long before the age period when the incidence of naturally occurring embolism is at its peak.[7] Lastly, in our experience, the statement itself is not true. We recognize embolism long after operation. The incidence is as yet below 1 per cent per year and is higher in those with atrial fibrillation. Our last case developed a fatal cerebral embolus three years after operation during a bout of atrial fibrillation that was not present previously.

Actually, the cardiac surgeon avoids thrombi that are adherent to the auricular wall for fear of producing embolism and thereby permits the threat of future spontaneous embolism to persist.

7. Fifty-six (39.7 per cent) died of congestive heart failure at an average age of 50.9 years. Of twenty autopsies in this group, only four had isolated mitral valve disease and only two of these were reported as stenotic by the pathologist. Only one individual died below the age of fifty years with isolated mitral stenosis and congestive heart failure, a woman of thirty-three years with advanced scleroderma.

From this analysis, it appears that isolated mitral stenosis is a rare cause of fatal congestive heart failure and when it does occur, tends to occur most commonly in the sixth decade. Furthermore, such deaths occur only in individuals with very large hearts and atrial fibrillation. All surgical deaths that occur in individuals without intractable right heart failure are attributable directly to surgery and the age of death can be used to gauge the probable loss of years of life. The average weight of the heart at death in this group was 643 grams. The heart weight in individuals who die after mitral valvotomy may also be used to determine whether premature death has occurred.

It is, however, true that most individuals who die of congestive heart failure have had symptoms for many years and, in our experience, generally for over a decade. The symptoms, their intensity and the incapacity of the patient may vary greatly, little, or not at all from time to time. Mitral valvotomy is based upon the concept that relief

of the impediment to blood flow through the mitral valve will relieve symptoms and incapacity. Unfortunately, the type of incapacity produced by mitral stenosis may be indistinguishable from that produced by mitral stenosis with significant mitral regurgitation and, indeed, by myocardial disease independent of the mitral stenosis that is present. For these reasons, we must not overlook the fact that there may be significant cost of operation due to error in diagnosis. The error even for the diagnosis of the predominant mitral valve pathology cannot, at the present time, be assessed because there is, as yet, no reliable technique for confirming, during life, the accuracy of the surgeon's interpretation of the tactile and kinesthetic sensations of his finger.

The major difficulty in evaluating mitral valvotomy is that it does not destroy the conventionally accepted findings of mitral stenosis. Our experience indicates that the clinical, electrocardiographic and roentgenologic findings in mitral stenosis are so rarely changed after operation, that, when changes are seen, we always search carefully for a transient event in the preoperative past to account for it. Most commonly, these are acute carditis in the younger individual and pulmonary infarction or infection in the older person. We have seen pulmonary infarction at operation totally unsuspected clinically or radiologically.

Indeed, it is more common for additional signs of mitral valve disease to appear after operation, the commonest of which is a systolic murmur or its increase. Most physicians regard this murmur as insignificant. If conventional criteria are used, a diagnosis of mitral regurgitation must be made. It is, of course, possible that surgical tears of the mitral leaflets produce systolic murmurs of no dynamic significance. However, we believe that mitral regurgitation is actually the cause for most of the murmurs, first, because there is no question of symptom-producing and even fatal mitral regurgitation, so that it is inconceivable that lesser grades of regurgitation are not produced; secondly, even though cardiac dynamics are considerably depressed during operation, regurgitant jets are produced or increased by the surgeon in at least 10 per cent of his operations; thirdly, giant P waves occasionally are seen temporarily immediately after surgery; fourthly, a notched widened P wave may first appear after surgery and persist; and, lastly, these individuals develop after surgery an apex impulse that is localized, forceful and visible, with a distinct thrust, a finding that, in the absence

of chest deformity, has always meant to us an increase in size of the left ventricle. These individuals may rarely show a decrease in the electrocardiographic evidence of right ventricular hypertrophy but this change is always accompanied by obviously increased and high R waves in the left precordial leads. Decrease in rightward deviation of the QRS vector may also occur in individuals who had sustained pulmonary infarction or pneumonia with or without pulmonary edema in the recent preoperative past or in those whose preoperative electrocardiogram was taken before complete dissipation of heart failure.

Because the conventional findings of mitral stenosis are not abolished by surgery, there has been a tendency to evaluate adequacy of operation on the basis of relief of symptoms or incapacity, a method that obviously begs the question of the significance of mitral stenosis and of the adequacy of restoration of mitral valve function and its value.

This fallacy is clearly demonstrated by the surgical production of permanent atrial fibrillation that occurs in approximately 10 per cent of individuals with preoperative sinus rhythm. It has been universally accepted that naturally occurring atrial fibrillation in individuals with rheumatic heart disease represents a more advanced stage of the disease than those with sinus rhythm and that those with atrial fibrillation are more likely to develop embolism and perhaps other complications. Yet, everyone includes individuals with surgically produced atrial fibrillation in the improved group, even though digitalis which had not been required before operation is now necessary. It may be that the surgical production of atrial fibrillation has a different prognosis than that occurring naturally. Certainly, though, it is too early to regard such individuals as improved regardless of how they feel. We believe that, regardless of so-called functional classification, no one who requires more cardiac therapy after operation should, as yet, be included in the group improved by surgery.

The importance of medical therapy can be clearly demonstrated by withholding it. Incidentally, many unoperated individuals with mitral stenosis and sinus rhythm have been unnecessarily maintained on cardiac therapy. Even individuals with atrial fibrillation may remain clinically symptom-free for years without digitalis. Apparently, troublesome fast ventricular rates are prevented by partial organic or functional block at the atrial-ventricular node. Such long continued cardiac therapy that had no relationship to the disappearance of pre-existing

symptoms has greatly complicated the evaluation of additional therapy, medical or surgical.

Another distressingly frequent effect of mitral valvotomy is the appearance, after a variable latent period, of a combination of events that in our experience does not occur in any other type of non-rheumatic cardiac or pulmonary surgery. The syndrome, characterized by a single bout or, more commonly, by recurrent bouts of pain and fever, with a variable incidence of pericarditis, transient atrial fibrillation or atrial tachycardia, prolonged atrial-ventricular conduction time, cardiac enlargement and cardiac failure, all indicating that the reaction is not limited to the pericardium and pleura, has been regarded by us and others as a reactivation of rheumatic fever.[9, 10] Some prefer the non-committal term, post-commissurotomy febrile syndrome. We have what appears to be indisputable evidence of its rheumatic nature, namely, fresh Aschoff bodies along the lines of incision both on the mitral leaflet and the pericardium. Some agree with our interpretation but regard the reaction as unimportant because they regard it as self-limited and without effect on the outcome of the operation. It is recognized today that spontaneous reactivation of rheumatic fever subsides with frequently no detectable increase in permanent cardiac damage. This recovery does not invalidate the diagnosis of recurrence of rheumatic fever but rather is attributed to resistance of the host, cardiac reserve and medical therapy. It is known that young individuals with active rheumatic carditis may show no progressive increase in heart size, if they remain at bed rest.[11] If the postoperative reaction has been intense enough to produce cardiac failure, it is our experience that the ultimate outlook depends upon the preoperative cardiac reserve. Individuals with preoperative intractable right heart failure remain permanently worse and require an intensification of the cardiac therapeutic regimen. Individuals with right heart failure that had cleared before operation have a 50 per cent chance of remaining in permanent right heart failure or require an intensification of therapy to keep them out of it. Individuals with left heart failure that had cleared before operation usually lose all signs of failure that appear after operation, unless excessive mitral regurgitation is produced. But, we believe that it is, as yet, too early to be certain, even in these instances, that reactivation of rheumatic fever was harmless, because even at the age of forty-seven years, ten years later than the average operative age, recovery from

spontaneous failure is compatible with life for many years in the majority of individuals. We are particularly concerned about its significance because we have recognized permanent cardiac enlargement in some of these individuals, the enlargement being predominantly in chambers proximal to the mitral valve.[12] On the other hand, cardiac enlargement that occurs after surgery is not always reflected in the functional state. Indeed, dyspnea may be relieved by latent right heart failure that becomes obvious if cardiac therapy is withheld. Furthermore, failure occurring months or years after surgery is frequently predominantly right sided. Dyspnea may be absent or a minor complaint although the patient may be obviously short of breath.

This brief review suggests that present day mitral valvotomy carries a higher mortality and morbidity than that which occurs naturally. It is hoped, as with all new surgical procedures, that, with increasing knowledge and better selection of patients, mortality and morbidity will decrease and be justified by the beneficial effects of the operation. It is important, however, that we have unquestionable evidence of surgically induced benefits.

At the very beginning of the present surgical era, it was recognized that a decrease in impediment to blood flow through the mitral orifice would be reflected in a decrease in pressure in the left atrium. Pressure changes at operation obtained at that time were highly variable both in degree and rarely in direction. Discordant changes were seen in systolic and diastolic readings. The degree of atrial distension at the beginning of ventricular contraction could not be assured.[13] It was soon realized that such changes could not be interpreted without knowledge of the pressures on both sides of the obstruction, namely the left atrial systolic pressure, the left ventricular end-diastolic pressure, and also of the cardiac output. The numerous difficulties in obtaining such readings that are reliable are obvious, but such studies are now being carried out, at least in part, in many clinics so that the immediate hemodynamic effects of the surgical procedure will have objective verification. However, even if the atrial-ventricular pressure gradient is decreased at operation without increase in the end-diastolic pressure in the left ventricle and without diminution in cardiac output, persistence of such changes are not guaranteed for several reasons. First, even though the rigid finger may be able to decompress the left atrium, the flow of blood may be inadequate to prevent after a variable time

the elastic properties of the valve from returning the leaflets to their pre-valvotomy position, an occurrence that is readily observed at times at surgery when the finger is withdrawn. So far as we can tell from our pathologic data, calcified leaflets regarded as adequately opened by the surgeon, may be in a position that makes the mitral orifice identical with similar valves that have not been subjected to operation. Secondly, subvalvular stenosis may be unrelieved by surgery. Thirdly, reactivation of rheumatic fever may nullify any potential benefits of operation for it is the viable and pliable mitral valve that may be the seat of fresh Aschoff bodies. Fourthly, mitral regurgitation even of minor degree produced by surgery may nullify beneficial effects of valvotomy. Lastly, changes by surgery in valve size or mobility may be unable to increase left atrial-ventricular flow, the crux of the problem in those with diminished left atrial-ventricular flow.

Most attempts to evaluate permanent effects of the operation on valve function are based upon the technique of right heart catheterization, the results of which are used to infer changes within the left atrium which in turn are attributed to change in valve size and mobility produced by the surgeon. The clinical physiologist is aware that these pressure pulses represent the end result of the interaction of many factors of which impediment to left atrial-ventricular flow is but one. Many acute self-limiting precipitating events can raise these pressures. The reliability of the interpretation of pressure changes will depend first upon the care with which such instances are excluded. Nor are we certain as yet of the time necessary for complete convalescence from such acute events.

Attempts to exclude abnormal pressure findings of myocardial failure from mitral block are based upon the response of these pressures and the cardiac output to digoxin given intravenously.[14] In our experience, the time interval of these studies is far too short to obtain the maximal beneficial effects of digitalis. Moreover, the salutary effects of physical rest itself have been largely ignored. Most important, not all types of myocardial failure respond to digitalis and one of these types is active rheumatic carditis. Sharp drops in cardiac function without obvious cause in individuals with rheumatic heart disease were, in the days before mitral valvotomy, always regarded as suspicious for active rheumatic carditis. Every large clinic has necropsy evidence to support such a diagnosis. Interpretation of pressure changes in such

instances may be very misleading. We have evidence at autopsy of diffuse rheumatic carditis in individuals who were subjected to mitral valvotomy because they had no clinical or laboratory evidence of infection and failed to respond to digitalis. Their only symptom was progressive dyspnea of several months' duration without fever, tachycardia or laboratory evidence of infection.

We are also uncertain of the significance of drops in pressure as the circulation slows or the heart enlarges. It is generally known that pulmonary artery pressure cannot be correlated with cardiac size or cardiac failure, two findings that have been valuable in evaluating prognosis. At this time, we still believe that enlargement of cardiac chambers after surgery outweighs any potential beneficial effects of drops in pulmonary pressure. It may be that transient rises in pulmonary pressure which recede partly as the heart enlarges may be the natural changes that occur as the heart deteriorates. Finally, many reports in the literature indicate that postoperative pulmonary artery pressures (and other numerical figures) may frequently be higher than preoperative pressures of other individuals in the same series. Yet, the first are regarded as indicating marked improvement and the second as requiring surgery. These findings emphasize the lack of correlation even between symptoms or clinical status and hemodynamic events. Indeed, good clinical results are reported in individuals whose pulmonary artery pressure fell, remained unchanged or even rose after operation. We do not understand how improvement can be attributed to mitral valvotomy in those individuals whose pulmonary artery pressure rises after surgery.

Significant obstruction at the mitral valve must be reflected in an increase in pressure proximal to the valve or a decrease in left atrial-ventricular flow or both. A decrease in pressure after mitral valvotomy in chambers proximal to the mitral valve is beneficial only if left atrial-ventricular flow is not simultaneously reduced. For this reason, we have turned our attention at this time primarily to methods that are concerned with left atrial-ventricular flow and the effects upon it of mitral valvotomy and other variables.

We use the biplane stereoscopic apparatus of Chamberlain, timed by the carotid pulse. Simultaneous views in two planes are needed to identify with certainty portions of the cardiovascular silhouette, to visualize opacification in specific regions and to estimate volume. Stereo-

scopy enhances accuracy and is of particular value in differentiating extracardiac densities that may appear to be within the heart on a single angiocardiogram. A mechanical rather than electrical timer is used because many electrical events, such as premature beats or other arrhythmias, may be ineffective in producing mechanical systole of the heart. Timing is necessary in assessing the significance of difference in opacification in serial roentgenograms and in determining the number of cardiac cycles required to fill or empty any portion of the heart. We use 50 milliliters of 70 per cent Urokon injected as rapidly as possible into an exposed antecubital vein. Anterior and lateral projections are used because of greater ease of constancy of reproduction not only in positioning of patient but also in identifying specific regions without overlapping. Roentgenograms are obtained every 0.7 second for at least 21 seconds. Subsequent roentgenograms are obtained at variable intervals depending upon the clinical evaluation of heart function and the radiographic determination of heart size. The tube is shifted at the time of exposure of alternate films to allow for stereoscopic pairs. The roentgenograms are analyzed for time of appearance and disappearance of opacity of the superior vena cava, right heart, pulmonary artery, left atrium, left ventricle and aorta. The degree of opacification is measured and corroborated by a densitometer. The results are plotted as density against time. Details of this study will be published elsewhere.[15]

In the normal individual, the time from the initial appearance of dye within the right atrium to the appearance of dye in the ascending aorta, which we call the intracardiac circulation time that represents the shortest time required for dye in detectable concentration to traverse the heart, is not greater than 6.3 seconds and always exceeds the right heart time. The right heart time, pulmonary artery time and left atrial times approximate each other and are each 5.6 seconds or less. Opacification of the pulmonary artery disappears before the ascending aorta is visualized. Left atrial density is not great and is poorly delimited. Indeed, dye opacifies clearly the pulmonary veins adjacent to the left atrium more than the left atrium itself and fuses quickly with the left ventricular density. The left ventricle is opacified usually in less than 0.7 second and never longer than 1.4 seconds after initial left atrial opacification.

These findings are in marked contrast to those in individuals with

mitral stenosis. In the absence of heart failure or marked cardiomegaly, the intracardiac circulation time may be prolonged but does not exceed 9.1 seconds. The right heart time is usually less than the intracardiac circulation time and rarely may equal it. The pulmonary artery time may be much longer than the right heart time and the pulmonary artery may remain visualized after the appearance of the ascending aorta. The left atrial time is 6.3 seconds or longer and almost always exceeds both the pulmonary artery and intracardiac circulation times. The left atrium is increased in size and its borders are sharply defined. Visualization of the left ventricle occurs within 0.7 second or may be delayed to as long as 2.8 seconds after initial left atrial opacification. Opacification of the left ventricle is sparse compared to that of the left atrium. However, the difference between left atrial and left ventricular density depends not only upon time but also upon the phase in the cardiac cycle that the roentgenogram is exposed. It is possible to have a series of roentgenograms without opacifying the ventricle once in diastole. Conversely, ventricular diastole may be visualized several times. Also, left ventricular opacification may be readily apparent in one projection and impossible to recognize in another. Finally, stereoscopy allows for recognition of dye within the pulmonary vasculature which appears to be within the left ventricle in a single angiocardiogram.

The finding in mitral stenosis of a left atrial time longer than that of the intracardiac circulation time and of the pulmonary artery time, which, in turn, in the absence of right heart failure, is usually longer than the right heart time, is visual evidence supporting the concept of a block at the mitral valve.

The angiocardiographic pattern of mitral stenosis which we have just described is, however, not diagnostic. A prolonged left atrial time and sparse opacification of the left ventricle may be seen in mitral stenosis with regurgitation or even in pure mitral regurgitation as diagnosed by the surgeon. A giant left atrium with marked regurgitation and minimal stenosis diagnosed at operation likewise gives the picture of an intensely opacified left atrium with delay and sometimes complete non-opacification of the left ventricle. No individual with clinically diagnosed pure mitral regurgitation was subjected to operation. Individuals so diagnosed clinically with but slightly enlarged left atria showed homogeneous opacification of the left atrium and left

ventricle. Otherwise, no relationship could be determined between left atrial time and left atrial size or between left atrial and ventricular opacification to differentiate the diagnosis of "pure" mitral stenosis from mitral stenosis and regurgitation as made at surgery or to predict the degree of mitral stenosis as reported by the surgeon. However, a lifting apical thrust was found in all individuals with large atria.

Indeed, the entire angiocardiographic pattern of mitral stenosis may occur in the complete absence of organic mitral valve disease. Apparently, non-valvular enlargement of the left atrium may in itself impede left atrial-ventricular flow. We have seen such findings in an individual with primary pulmonary artery disease, proved at autopsy.

However, the possibility of occult left ventricular failure in this instance could not be excluded, because it is easy to show that left ventricular failure of any cause, be it aortic valve disease, systemic hypertension or coronary artery disease, may produce the left atrial pattern of mitral valve disease. The distinction between the two is, however, easy, because of the thickness of the left ventricular wall, increase in degree and duration of left ventricular opacification and with aortic disease frequent eccentric opacification of the aortic orifice. Additional mitral stenosis, however, if present, would be difficult if not impossible to detect by angiocardiography.

These findings visualize the clinical physiologist's pressure findings in left ventricular failure but frequently precede them because such changes are seen before clinical failure is recognizable.

Indeed, in our experience, the angiocardiographic pattern of mitral stenosis precedes abnormal pulmonary artery or pulmonary artery wedge pressures. It is for this reason that we believe that slowing of the circulation may occur before rises in pressure or may persist after pressure falls.

It is clear that angiocardiography, like other techniques, is not specific for mitral stenosis and that impediment of left atrial emptying, as determined by this technique, can occur in those with mitral valve disease, regardless of whether stenosis, regurgitation or both are present and can occur even in the absence of organic valvular disease.

Although the angiocardiographic pattern is not specific for mitral stenosis, it was hoped that mitral valvotomy would abolish or decrease the impediment to blood flow in individuals who did have mitral stenosis as visualized by this technique. Our studies, however, indicate

that present day surgery for mitral stenosis cannot abolish impediment of left atrial-ventricular flow as visualized by this technique, nor are there any characteristic angiocardiographic features, other than absence of the left auricle or presence of thoracic surgical incisions, that can differentiate those who have had mitral valvotomy from those who have not. Any change is a purely qualitative one. We have already indicated, however, that impediment of left atrial-ventricular flow of similar magnitude may be due to many factors other than mitral stenosis. It is important that qualitative changes in left atrial-ventricular flow due to treatment of these factors should not be interpreted as due to surgical treatment of mitral stenosis.

The significance of medical therapy in reducing impediment of left atrial-ventricular flow can be shown in some individuals who have already had their mitral stenosis reduced by surgery. An intensified medical regimen in individuals with congestive heart failure or even with dyspnea alone may shorten all circulation times, disproportionately shorten the left atrial time and increase degree of left ventricular opacification.

This last change with medical treatment indicates that the pattern of mitral stenosis in the same individual is more often seen in failure than in compensation, evidence of the importance of myocardial function in left atrial-ventricular flow. Changes of this sort are most quickly made by mercurials and increased digitalis and may be accomplished by digitalis alone or even by bed rest without other change in cardiac therapy. But, maximal changes take time and, in our experience, at least six weeks and possibly longer. Such changes can, at times, be demonstrated even in the absence of clinical evidence of heart failure and with an apparently adequately controlled ventricular response to digitalis in individuals with atrial fibrillation.

Mitral valvotomy, therefore, not only cannot abolish left atrial-ventricular block but also cannot be evaluated unless all other medication is kept constant. Indeed, the problem is even more difficult because some disabilities respond only to rest and time, such as carditis, pulmonary infarction and even infection. It is for this reason that we have stressed the need in interpreting the effect of mitral valvotomy for static disability maximally controlled by medical therapy.

Because of the present day attitude, it is difficult to obtain adequate controls. But, whenever the individual appeared stabilized clinically for

at least one month, we have, as yet, not observed any improvement in left atrial-ventricular flow comparable to that seen with medical treatment.

Of thirty individuals who regard themselves as improved after operation, nine had atrial fibrillation and large hearts estimated above 600 cc. before operation. All have persistent and markedly prolonged left atrial and pulmonary artery times. Three of these greatly exceed their preoperative times. Pressure studies in apparently comparable individuals have shown variable and usually slight changes. Even if marked drops in pulmonary artery pressures are obtained, it is difficult to interpret their significance because it is in these larger hearts that angiocardiography, in the immediate postoperative period, may demonstrate a significant increase in size of the pulmonary artery and of the right atrium and right ventricle with slowing of the intracardiac circulation, and with decreased opacification and, at times non-opacification of the left ventricle. These findings persist. They may not be reflected in recognizable manifestations but this type of individual represents one we have previously described who may develop clinical right heart failure after operation. These patients, although worse, may genuinely feel better because troublesome dyspnea has been replaced by right heart failure, the clinical manifestations of which, if present, may be controlled by mercurial injections. Indeed, right heart failure may be present in individuals who deny ever having had dyspnea. Right heart failure may not be recognized on conventional films. Because of the apparent decrease in pulmonary vascular markings, the radiologist might interpret the increased heart size as due to increased left ventricular filling. Yet, angiocardiography reveals marked slowing of the circulation through the right heart and pulmonary artery, and no dye within the left ventricle. In this type of failure, the jugular veins are prominent and fill rapidly from below. An elevated venous pressure may be demonstrated by abdominal compression.

Two with only slightly enlarged hearts developed permanent atrial fibrillation and more prolonged left atrial and pulmonary artery times after surgery.

Three had atrial fibrillation with slightly enlarged hearts. Two of these had persistently long left atrial and pulmonary artery times. The other, who appears to us considerably better clinically, has a prolonged left atrial time but a normal pulmonary artery time.

Sixteen had hearts of normal or slightly increased size with sinus rhythm. Of these, six have persistent markedly prolonged left atrial and pulmonary artery times. Ten have persistent slightly prolonged left atrial and pulmonary artery times. We could not distinguish these last two groups on clinical grounds. One patient who stated she had one block dyspnea for over six months, uninfluenced by digitalis, had a pliable mitral valve that was easily adequately opened and now leads an entirely normal life. However, she has a persistent right heart time of 11.9 seconds, a pulmonary artery time of 12.6 seconds and a left atrial time of 14 seconds. A retrospective history raised the possibility of preoperative psychogenic dyspnea engendered by the present surgical climate. She had forced her doctor to consent to operation and we agreed because of unequivocal findings of pulmonary hypertension. She was catheterized four days ago, ten months after operation. Her right ventricular pressure is 50/8 mm. Hg and her pulmonary artery pressure is 52/30 mm. Hg. From these studies, it appears that, in contrast to myocardial function that has an obviously potent effect on left atrial-ventricular flow, mitral valvotomy has none or one too feeble to be detected by our technique. Mitral valvotomy, on the other hand, may permanently decrease left atrial-ventricular flow in individuals with a large heart and in individuals who develop permanent atrial fibrillation. In the individual with mitral stenosis and a small heart, near normal circulation times may be maintained by a disproportionately high pressure proximal to the obstruction. The main purpose of mitral valvotomy is to permit such flow to continue at more nearly normal pressures. However, near normal times in individuals with mitral stenosis may be present with normal or near normal right ventricular, pulmonary artery and pulmonary artery wedge pressures.

For these reasons, we believe, at the present time, that the first responsibility of a physician when confronted with an individual with mitral stenosis, is to determine if symptoms are due to self-limiting or medically treatable events. If in doubt, there is hardly ever any urgency to operate. Our angiocardiographic studies suggest, on the basis of comparison with conventional films, some of which were taken as long as twenty years ago, that mitral block, in the absence of precipitating events, changes so slowly, if at all, that for practical purposes it may be regarded as stationary for years. Even repeated attacks of pulmonary edema are compatible with long intervals of freedom from

symptoms and need for cardiac therapy. Thus one individual had pulmonary edema twenty years ago during her first pregnancy, eight years ago during her fifth pregnancy and one month before the present study while rushing home from a party. Between attacks she had no symptoms and no cardiac treatment. Her intracardiac circulation time is 7.7 seconds, her right heart time 4.9 seconds, her pulmonary artery time 6.3 seconds, her left atrial time 7 seconds. Her right ventricular pressure was 45/3 mm. Hg and her pulmonary artery pressure 45/22 mm. Hg.

The second responsibility of the physician is to determine if simple precautionary measures do not produce a comfortable and satisfactory life for the individual's age, social and economic status. If not, and pulmonary artery pressures are high, mitral valvotomy may be advised but not urged.

Mitral valvotomy should never be urged because it is only those with normal or slightly enlarged hearts and no roentgen-ray evidence of calcification of the mitral valve who possibly may be benefited. These individuals have the best natural prognosis so far as the ultimate development of congestive failure is concerned. It is rare for them to die before the sixth decade. Surgery, on the other hand, has even in this group an immediate mortality of at least 4 per cent, and at least 2 per cent chance of embolism in those who are fibrillating and survive operation and a 5 to 10 per cent chance of the production of permanent atrial fibrillation. Moreover, the diagnosis may be wrong. The operation never destroys mitral block completely and indeed is rarely effective in individuals with densely fibrotic and motionless valves. Finally, the duration of benefit, if any, is as yet unknown and involves the concept of restenosis.

Mitral block is never abolished by present day surgery. The clinical concept of restenosis is, therefore meaningless. The degree of mitral block may increase with time after surgery but the cause for this increase is conjectural. We do know from pathologic studies that the incisural surfaces of calcified, fibrotic and motionless valves do not reseal up to five years. But, from the obstructive standpoint, it makes no or very little difference if these surfaces reseal or remain permanently separated from one another by a distance equivalent to the thickness of the surgeon's knife or gape widely after finger fracture.

Restenosis has been used by many as synonomous with reappear-

ance of symptoms. Reappearance of symptoms after operation may appear for the same reasons that they occur before operation. Active carditis, arrhythmias, infection, pulmonary infarction, and excessive physical strain are common causes. Symptoms will depend upon the interaction of these precipitating events and the cardiac reserve. It is hoped that the earlier in the life history of rheumatic fever mitral valvotomy is done and the smaller the heart, the longer will the patient remain free of symptoms after operation because this is indeed true for the individual without surgery.

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HEADACHE: ITS ETIOLOGY AND MANAGEMENT

*Transcription of a Panel Meeting on Therapeutics**

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MODERATOR MERRITT: The subject for discussion this afternoon is headache. We have a panel of experts to discuss various aspects of the question. Unfortunately the subject is so broad that time does not permit us to bring to you all of the experts who would be needed to cover it fully.

Headache is one of the most common symptoms to which man is subject. There are few individuals who have not suffered from headaches on several or many occasions. Headaches may occur without any organic pathology or they may be a manifestation of serious disease. In the majority of cases headaches are transient and their occurrence can be directly related to an acute febrile episode or some other definite cause. The situation is different, however, in those cases where the headaches are chronic or occur at intervals over a period of months or years. It is important in these cases to determine by thorough study the underlying cause of the headache in order to correct any serious pathology. Headaches are a common manifestation of intracranial tumors, infections, head trauma, febrile illnesses, arterial hypertension, cerebral arteriosclerosis, cerebral anoxia or asphyxia of any cause.

All of the above enumerated conditions account for symptoms in only a small number of patients who consult their physician for chronic headaches. In many of these a thorough study will not reveal any significant finding which will explain their headaches. In the majority of patients with headaches of unknown cause, the symptoms are due to migraine or related to psychological tension. The pain-sensitive structures in the head are tissues covering the cranium, the large intracranial venous sinuses and their tributaries, the dura mater at the base of the skull, the dural arteries, the large arteries at the base of the brain, the 5th, 9th and 10th cranial nerves and the upper cervical nerves.

The substance of the brain, the small arteries on the surface of the cortex and the dura over the convexity of the brain are all relatively insensitive to pain.

Stimulation of the pain structure on or above the tentorium results in pain or headache in front of a line directly drawn vertically from the ears across the top of the head. This pain is transmitted by the 5th nerve. Stimulation of pain structures below the tentorium causes pain behind the line described and is transmitted by the 9th and 10th cranial nerves, and the upper three cervical nerves.

With this brief introduction, I would present to you the members

of the panel who will discuss the aspects that are appropriate to their specialty.

Our first speaker this afternoon is Dr. Daniel C. Baker, Jr., Associate Clinical Professor of Otolaryngology, College of Physicians and Surgeons, Columbia University, and Associate Attending Otolaryngologist, Presbyterian Hospital.

DR. DANIEL C. BAKER, JR.: The nose and the sinuses are considered by the lay person to be the most common cause of headache. The otolaryngologist is frequently consulted by the patient before any other physician sees him. In taking a routine history of a patient, regardless of the nature of his illness, if the question is asked, "Do you have headaches", the patient will usually reply "Yes". If you ask the patient what he thinks the cause of the headache is, he will say he has a "sinus".

In our civilization most people have some complaints relative to their nose and throat. Nasal blockage, sneezing, postnasal discharge, clearing the throat and cough are common symptoms. Humidity, temperature changes, heat and cold, dust, chemical content of the air, allergic factors, tension, mental fatigue, excessive smoking and other things may cause nasal symptoms. These symptoms represent the reaction of the individual to his environment.

It is possible to have extensive sinus disease and nasal disease and not have the symptom of headache.

In order to understand why the sinuses are thought to be a cause of headache, a knowledge of the anatomy of the paranasal sinus system is necessary. At birth the maxillary sinuses are already present and so are the ethmoid cells. The frontal sinuses are present after the first year of life and the sphenoid sinuses hollow out of the sphenoid bone in the fourth year. In a six year old child the sphenoid sinus has already taken on a definite relationship with the cavernous sinus and its combined structures.

On the lateral wall of the nasal chamber, the inferior turbinate has large venous spaces. It is this vascular tissue that causes nasal blockage and headache, when it is congested. There is a small amount of this tissue in the middle turbinate. All of the anterior group of ethmoid sinuses drain into the middle meatus which is covered by the middle turbinate. Any blockage of drainage or any interference with ventilation can cause headache.

The sphenoid sinus has a definite relationship with the optic chiasma and the hypophysis. There are numerous dehiscences in the lateral wall of the sphenoid sinus.

The nasopharynx is a common location for carcinoma to develop. There is an anaplastic type of cancer (Schmincke's tumor) which instead of growing out into the nasopharynx will grow into the different recesses and also the foramina at the base of the skull. It is an invasive type of carcinoma which causes very severe head pain along the branches of the first, second and third divisions of the fifth nerve.

The interior of the nose is innervated by the anterior ethmoidal and the maxillary portion of the trigeminal nerve. The posterior part of the nasal cavity, including the nasal septum gets the major portion of its nerve supply from the second division of the fifth nerve by way of the sphenopalatine ganglion. These nerves pass through the sphenopalatine ganglion to their distribution. Nerves from the ganglion pass not only to the nasal cavity, but also down the descending palatine canal across the hard palate and then branch upward into the anterior part of the nose through the foramina in the premaxillary wings. The vidian nerve, which is a branch from the carotid plexus and also the facial, joins the sphenopalatine ganglion. It passes through the lateral wall or the floor of the sphenoid sinus.

The teeth can cause the symptoms of sinusitis and headache. The upper three molar teeth always have a relationship with the sinus, and the fangs of these teeth project into the floor of the sinus.

The sphenoid sinus has a close relationship with the cavernous sinus, optic chiasma, optic nerves and the hypophysis. For this reason sphenoid sinusitis was thought to be a cause of optic neuritis, and sphenoid surgery was immediately performed regardless of whether the patient had any findings of sphenoiditis. A few of the patients did get well.

The nasal conditions which may cause headache are those that produce pressure. Marked deviation of the nasal septum and polyps in the nose large enough to cause pressure may cause unilateral headache. One should never expect a deviation of the septum to the left side or polyp in the left side of the nose to cause headache on the right side.

Sinusitis itself may cause headache. If the infection is an overwhelming one and the ostia, the normal drainage tract of the sinus is blocked off, then pressure can be built up within the sinus causing headache. Pressure can develop within the sinus from a cyst or from a tumor

or actual invasion of the sinus wall, or destruction of bone by a carcinoma, such as a Schmincke's tumor. The headache must be on the same side as is the disease.

There are other factors beside the nose and the sinuses which may cause headache that are related to the ear, nose and throat. There is the so-called sphenopalatine ganglia neuralgia, which has a wide distribution. For many years it was the practice of otolaryngologists to remove or to exenterate the sphenopalatine ganglion when patients complained of unilateral head pain. More recently, the ganglion has been injected. It is not known why the procedure helped a few patients.

Glossopharyngeal neuralgia is a pain which usually starts at the root of the tongue and is referred to the ear. A large styloid process may cause similar symptoms. There is a syndrome which occurs when the geniculate ganglion is disturbed and bleb-like formations occur on the drum and the canal wall with an associated facial paralysis. Usually there is a severe headache on the same side.

It is very seldom that the otolaryngologist finds a cause for headache in the average patient. Nasal disease and sinus disease are seldom the cause of chronic headache in my experience.

MODERATOR MERRITT: The second speaker on the program is Dr. Frank Payne, Assistant in Ophthalmology, College of Physicians and Surgeons, Columbia University; Assistant Attending Ophthalmologist, Institute of Ophthalmology, the Presbyterian Hospital.

DR. FRANK PAYNE: It is true that the ocular examination often reveals signs such as papilledema, visual field defects and muscle palsies which are of great importance in diagnosing headaches due to intracranial diseases. I shall limit my remarks, however, to the headache and head pain due to diseases or abnormalities of the ocular apparatus.

Regarding the incidence, it is difficult to state how often headaches are due to the visual apparatus. Patients usually go directly to the oculist without first consulting the general physician, because the public knows that the eyes may be the cause of headache. Also, it is relatively easy for the patient to undergo an eye examination.

Two questions confront the general physician: 1) Which patients should be sent to the oculist? and 2) What are the relations between ocular headaches and the patient's systemic condition? Certain general principles may help in answering these questions.

The most common causes of severe ocular headache are acute congestive glaucoma and acute iritis. Even today these diseases, if accompanied by nausea and vomiting, are occasionally mis-diagnosed as acute disease of the gallbladder and are referred to the general surgeon before the eye is recognized as the cause of the symptoms.

The less severe and chronic, recurring headaches are due usually to refractive errors, anomalies of the accommodation and convergence mechanisms, and muscle imbalances. We do not expect the non-oculist to recognize these conditions if of low degree, but it is interesting and very significant that severe symptoms are commonly due to *small* errors of refraction, and *small* degrees of muscle imbalance; and they are the most difficult to detect. Apparently, an individual does not make the continued effort to overcome the large refractive errors and muscle imbalances and thus does not develop eye fatigue or a feeling of strain; he will, however, make the effort repeatedly to overcome the small errors, and headache ensues.

To suspect the eyes as the cause of a headache, certain things are worth knowing. The level of visual acuity does not indicate whether or not the headache is of ocular origin. A good acuity may be attained in the presence of a high degree of astigmatism; or, a patient may have a very low acuity and yet not have a headache. Thus, the presence of good vision does not exclude the eyes as the cause of the headache.

These ocular abnormalities are causing an increasing incidence of headaches because of the nature of our modern civilization. When we reflect that most of our civilization has evolved and has been designed upon the unconscious assumption that every adult has 20/20 visual acuity, and the ability to read fine print, we realize that the ocular demands are stringent. Our world is mostly within two feet of our face in our occupations and pleasures. Publications of all kinds are employing fine type which frequently is too small to be seen by older individuals. Since people are living longer lives it will become increasingly important for publishers to use print-size compatible with the visual acuity of older individuals. Television, colored movies and other entertainments add more demands upon our eyes. Whether or not an ocular anomaly is the cause of a patient's headaches can be determined first by finding that anomaly, and then correcting it. Two individuals may have an equal error of refraction and yet one individual has headaches and the other does not.

The patient's general state of fatigue, his temperament, and his visual requirements influence the role of the ocular anomaly. Often a person develops symptoms at the end of a school year, and then becomes comfortable during the summer's vacation.

Patients convalescing from serious systemic illnesses often have headaches when reading to pass the time pleasurably. Ocular fatigue and headache necessitate glasses, at least temporarily. It is wise to minimize the time that a patient may devote to reading when recovering from a systemic illness. This is of particular importance in children.

Another factor in the use of the eyes has to do with the illumination. I see many patients whose ocular symptoms are attributable to the fluorescent type of lighting. Fluorescent light is being installed in schools, factories, institutions and public buildings. In my sincere opinion it is the most inferior, most obnoxious and ugliest type of light ever devised. Architects and interior decorators would improve our world tremendously if they would return to the use of the ordinary type of incandescent light.

In conclusion, I believe that it is wise to advise an examination of the eyes in most cases of headache. The ophthalmologist should not conclude that an ocular anomaly is necessarily the cause of the headaches, but must consider also the patient's habits, general physical condition, ocular requirements and environment, and cooperate with the general physician to determine the true cause of the headaches.

MODERATOR MERRITT: Our third speaker is Dr. Arnold P. Friedman, Associate Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University; Attending Physician, Neuropsychiatry, Montefiore Hospital.

DR. ARNOLD P. FRIEDMAN: *Introduction:* The two most common headaches that confront the physician are migraine and tension headache (muscle contraction headache). In recent years new data have been made available through experimental and clinical investigation which have given the physician a better understanding of the diagnosis and treatment of migraine and tension headache.

Migraine

A. Cause: The underlying causes of migraine are unknown. Many theories have been advanced but the large variety of precipitating fac-

tors and diversity of symptoms make it most difficult to explain all cases of migraine on any single etiologic basis.

Endocrine disorders, vitamin deficiencies, ocular malfunctions, trauma to the head and neck, allergy, hepatic disorders and cerebral anoxia have been proposed as the etiologic mechanisms in migraine headaches, but evidence to support these theories is lacking. A more tenable hypothesis is the inability of such patients to react adequately to stress for two reasons:

First, there is a hereditary factor; the mechanism through which this hereditary factor operates has not been clearly elucidated, but is possibly related to an imbalance of the autonomic nervous system. Secondly, they have an insecure personality pattern which interferes with their adjustment to their environment. This sets a pattern of function which the limited physiologic capacity of the individual is unable to handle, resulting in cranial vascular changes which produce the headache.

B. Mechanism: 1. Physiologic—Well substantiated observations from various sources have demonstrated that in an attack of migraine the following physiologic changes occur. An initial vasoconstriction of certain intracranial branches of the internal carotid artery produces visual and possibly other pre-headache phenomena prior to the onset of the headache. This prodromal period is followed by dilatation and distention of cranial arteries, primarily in the distribution of the external carotid artery. Stimulation of pain-sensitive nerves in and around the dilated vessels by the increased amplitude of pulsation is the presumed cause of the headache. Persistent dilatation results in a rigid, pipe-like state of the vessels. The pain at this stage is a steady ache replacing the earlier throbbing, pulsating type. During or following this, there is contraction of the neck muscles and "muscle-contraction pain" develops. This spasm of the muscles is a reaction to the initial pain and may outlast it. The initial phase of the headache is due to stimulation of pain endings which lie in or near the walls of the intracranial arteries, whereas the latter or "muscle-pain" is probably the result of either direct stimulation of nerve endings or ischemia of the muscles. Although in migraine the immediate cause of pain is associated with dilation of cranial arteries, it is evident that dilatation of blood vessels alone is not sufficient to produce headache. Other dynamic or chemical factors as yet not clearly delineated must contribute.

2. Psychologic—The importance of psychologic factors in the migraine attack is great. Personality studies have indicated that many patients with migraine are meticulous, neat in appearance, rigid in their thinking, and excessively aggressive toward their environment. It is often noted that in their earlier life they have had considerable insecurity with resulting tensions which are manifested in inflexibility, overconscientiousness, meticulousness, perfectionism and resentment.

In a recent study it was observed that psychodynamic mechanisms play an important role, even in migraine of young children. The types of neurotic symptoms observed in children were varied and dramatic. They included temper tantrums, phobias, frequent nightmares, hair-pulling, enuresis, obvious anxiety, hyperactivity, lethargy, thumbsucking, nailbiting and feeding difficulties.

In patients of all ages a variety of psychogenic factors have been related to the headache. Attempts have been made to define specific personality patterns. In our experience the personality make-up in these people is extremely variable and may be influenced by a variety of emotional factors. Most of these are unconscious and include hostility, identification with a family figure, a wish to remain in a position of dependency, or a desire to gain love, affection or attention. The most frequent conflicts are apparently concerned with hostile impulses associated with feelings of guilt.

There is little evidence of specificity of the precipitating psychodynamic factors. Not all patients with migraine are compulsive, perfectionistic or rigid. A recent objective psychologic evaluation of our patients confirms this point of view. Repressed hostility is an extremely common factor among many persons who do not have migraine but may have hypertension, ulcers or just a small bank account. Nevertheless, an understanding of the underlying psychologic factors plays an important part in the management of migraine, for in the ability of the patient to handle emotional tension lies the most satisfactory means of preventing the attacks in the majority of cases.

C. Characteristics: Migraine may be defined as that form of headache which is characteristically paroxysmal, periodic, unilateral, and throbbing. The headache occurs against a background of relative well-being, is often preceded by visual or psychologic disturbances, and is usually associated with vomiting and irritability. Frequently there is a history of similar headaches in the parents or other members of the

family.

The clinical picture of migraine indicates widespread bodily disturbances. Although attention is usually first called to the headache, there are numerous other symptoms to be considered as part of the entire picture. Among these are visual disturbances, including photophobia, autonomic disturbances such as pallor and sweating, edema of lids and extremities and difficulty with memory and concentration.

D. Objective Evaluation of Patients: General physical and neurological examinations are usually non-contributory. Routine laboratory studies such as blood counts, urinalysis, and skull roentgenograms are equally unrevealing. Ophthalmologic evaluation, including visual field studies, only rarely revealed any disorders. In our patients no striking variation from the normal electroencephalogram was noted in most cases, although Dow and Whitty indicate that a large number of abnormal records without specific patterns occurred in their migraine patients. Engel and his associates were able to demonstrate electroencephalographic changes accompanying the prodromal visual scotomas.

We were unable to find any relationship between fluid retention per se and the development of headache, nor were we able to relate migraine to a dysfunction of the pituitary adrenal system on the basis of eosinopenic response. Measurement of the volume changes occurring in the external carotid circulation in patients with migraine by use of the glycerine-pellotte and photo-electric cell technique gave us methods of recording objectively the changes in the external cranial circulation prior to and during the headache. Our observations with these tests indicated that the increase of the pulse wave amplitude was related to the severity of the migraine attack and following the use of a vasoconstrictor (ergotamine) there was a diminution of the pulse volume with a concomitant reduction in headache.

Tension (Muscle Contraction) Headache

A. Cause: The actual cause of tension headaches is unknown. However, there is good evidence that they are related to psychologic disturbances. In a majority of our cases the fundamental psychic factors were largely unconscious, although most patients were aware of their anxiety. Environmental demands of an economic, social, physical or intellectual nature beyond the capacity of the patient's personality may also produce somatic response of which headache is the major

symptom. As in migraine the most frequently observed conflicts in cases of tension headache were those over hostile impulses. These patients demonstrated aggression, hostility and intense resentment against members of their family or persons who represent family figures. However, there is little evidence of specificity of the precipitating psychodynamic factors and as noted in migraine they may include identification, wish to remain in position of dependence, means of gaining attention, and so on. Although these findings help us to understand the mechanism of certain headaches, they do not elucidate the cause. Why the same psychogenic factors previously discussed as initiating headaches through physiologic mechanisms may also produce them on a purely psychologic level, such as in conversion mechanisms, is unknown. Furthermore, the same type of psychologic conflict may produce a variety of symptoms, such as headache, ulcers and hypertension, or may be present in an individual who is symptom-free.

Our present knowledge indicates that in tension headache, emotional conflicts which the patient has suppressed or repressed because of their unpleasant nature may produce a discharge, either skeletal or autonomic, with resultant changes in the muscles and blood vessels of the head and neck eventually productive of pain. The end organs for pain near these muscular and vascular changes are stimulated and create nerve impulses that pass along the afferent system to the central nervous system, where they are translated as painful sensations.

Muscular headaches differ from tension headaches in that the former occur with local muscle or nerve root injury, and secondarily, from noxious stimulation elsewhere in the head. The clinical features of the conditions causing the muscle spasm, for example, cervical disk, osteoarthritis, cord tumor, ocular inflammation, and so on, usually serve to differentiate these types of muscular headache from spasm associated with emotional tension.

B. Mechanism: In tension headaches muscular or vascular mechanisms may act independently or concomitantly. With muscle tension, sustained contraction of the skeletal muscles of the head and neck causes pain or dysesthesia in the neck and scalp. Associated with these muscular spasms may be ischemia which could be a contributory or primary factor in the induction of pain. It has been also hypothecated that excessive concentration of potassium in muscle from ischemia or sustained contraction stimulates the chemoreceptors in the tissues. An-

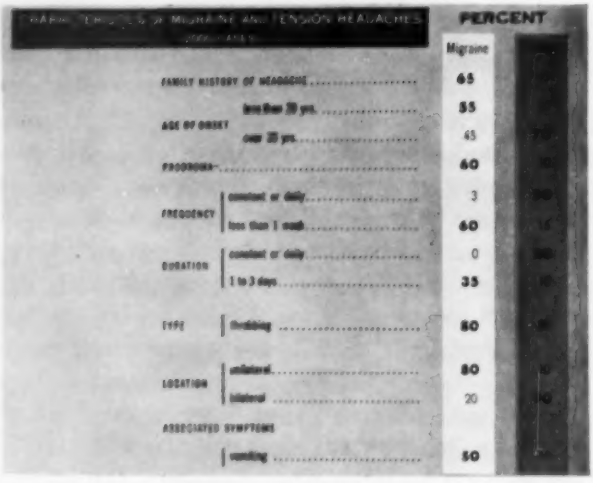

Fig. 1.—Migraine and Tension Headaches did not differ significantly in respect to the following: incidence, sex, precipitating causes, occurrence (time of day or season), mood change, onset and termination (abrupt or gradual).

other factor responsible for the head pain may be a central spread of the excitatory effect of noxious stimulation of the soft tissues of the neck. This spread of pain is carried by the upper cervical nerves and may produce painful sensations in the forehead and face.

Under stress a discharge may occur in the autonomic nervous system with resultant changes in the cranial blood vessels. The end organs for pain surrounding these blood vessels are stimulated and create nerve impulses which pass along the afferent pathways to the central nervous system.

C. Characteristics: Tension headache is that type of headache occurring in relation to constant or periodic emotional conflicts concerning which patients are partially aware. Tension headaches have no prodroma, are usually bilateral, occipital or frontal, and may be accompanied by a variety of associated signs, including anxiety, nausea and vomiting. Frequency and duration are variable.

D. Comparison of Migraine and Tension Headache: In comparing migraine and tension headache certain clinical features appear to be characteristic of each, although there are wide variations in each group and the same individual may have both types of headaches (Figure 1).

E. Differential Diagnosis: It is important to differentiate migraine and occasionally tension headache (muscle contraction headache) from other clinical conditions in which headaches are associated.

Tumors, particularly angiomas which most often appear in the parietal-occipital region, may lead to attacks of headache, nausea and vomiting, sometimes associated with visual hallucinations. Often convulsive seizures are part of this picture, and sooner or later intracranial pressure may develop as the tumor exerts pressure or encroaches upon neighboring parts of the brain. Sometimes in the case of angioma a cranial bruit may be heard. Migraine may simulate or be simulated by an aneurysm of the internal carotid artery which presses on a nerve. Persistent field defect and reduction of visual acuity or extraocular palsies may be associated with other focal signs in the case of the aneurysm.

Headache associated with temporal arteritis may occasionally be confused with migraine.

Transitory attacks of paresthesia, weakness and aphasia may occur in migraine without headache. Differentiation of this from disseminated sclerosis or cerebral vascular lesions may at times be difficult. Of course, headaches occurring alone must be distinguished from pain in the head due to other causes. In such headaches we must distinguish the various neuralgias, neuritides, diseases of the bones of the cranium, subdural hemorrhage, meningeal irritation, fibromyositis, etc.

Although rare, migraine is occasionally confused with glaucoma. The importance of measuring the intraocular pressure in headache patients cannot be over-emphasized.

Treatment

Treatments of migraine based upon a multiplicity of etiologies are remarkable for their consistent therapeutic success. In our experience the following is the most effective treatment for migraine:

1. Symptomatic—Symptomatic treatment of migraine is most effective by use of oral or rectal ergotamine tartrate and caffeine (Cafergot). Rectal use of Cafergot has proved empirically to be most efficacious, especially when oral medication cannot be retained. It is likely that rectal medication has the advantage of being absorbed more directly into the systemic circulation, without having to penetrate the hepatic and gastric barriers. Hence it is postulated that its action is quicker

with less side effects than by oral administration. This requires further investigation.

In some patients ergotamine tartrate is poorly tolerated and the use of dihydroergotamine methanesulfonate (D.H.E.-45) is indicated. Dihydrogenation of ergot reduces the vasoconstrictive action. In order to produce an equivalent therapeutic effect dihydroergotamine must be given in doses twice as great as ergotamine tartrate. It can only be administered parenterally, and like ergotamine, must be given as early as possible in the attack. Efforts to abort the attack in the prodromal phase by the use of vasodilators such as amyl nitrite, nicotinic acid, oxygen and B-methylacetylcholine (Mecholyl), etc., have been uniformly unsuccessful.

Analgesics and sedatives are sometimes indicated if the headache has been present long enough for edema to take place and the vessels to become firm and tortuous.

2. Prophylactic—It is well known that suitable psychotherapy may be of great value in reducing the intensity and number of migraine attacks in most patients and may even result in their disappearance for a considerable time.

Adequate relaxation, improvement in sleep and correction of any physiologic abnormalities will be of help in reducing the frequency of the attacks. In a few cases there may be evidence that the precipitating mechanism is allergic, endocrine, or "metabolic". It has been my experience that these factors are too isolated to be of real value in therapy. However, when an offending allergen is responsible it should be removed or the patient desensitized. If the onset of migraine is associated with the menstrual period the use of progesterone or testosterone, or both, may be helpful. Occasionally, a diet that restricts the daily intake of salt in addition to a diuretic seems to be beneficial.

The use of such drugs as histamine, nicotinic acid, etc., in my experience, is of no value. Sedatives to reduce emotional tension are limited in their usefulness. More recently we have used reserpine and Thorazine as interim treatment with migraine patients. Our results have not been encouraging.

Periodic and often paroxysmal nature of migraine and other types of vascular headache brought forth the idea that treatment with anticonvulsants might be of value in these disorders. Of the anticonvulsant drugs, two which we have had experience with are Dilantin and Mesan-

toin. Both are hydantoinates. These are analogous to the barbiturates, being derivatives of glycolyl urea as compared with malonyl urea. A small number of migraine sufferers respond well to Mesantoin, or Dilantin prophylactically. This limited group consists of patients who have an aura of aphasia, paresthesias, hemiplegias prior to the headache and an abnormal electroencephalogram. In certain other cases where there is a family history of migraine and epilepsy and an abnormal electroencephalogram, the use of certain anticonvulsant drugs is of value in controlling the headache. Dilantin and Mesantoin are administerd orally.

Tension Headache

1. Symptomatic treatment—Symptomatic relief from tension headache is secured by drug therapy, which as in psychotherapy, must have flexibility for its keynote. The treatment of tension headache is nonspecific, but the purpose of therapy is to relieve tension and raise the pain threshold. This is best accomplished by use of an analgesic-sedative combination. Such a combination should react with the minimal side effects allowing the patient to maintain his environmental relations and not be a problem because of addiction potential or development of tolerance.

2. Prophylactic treatment—Control of tension headaches can best be accomplished by use of psychotherapy, for this is the only method in which the patient's emotional conflicts can be resolved.

The use of one per cent procaine directly into the tender areas of the neck may eliminate the headache for several hours or a few days. Its long term use in tension headache is not consistent with the underlying mechanism causing the headache.

The use of sedatives such as barbitals and analgesics is only of temporary effect. Furthermore, their side effects curtail prolonged usage.

More recently we have used reserpine and chlorpromezine with patients with tension headache. Preliminary study indicates that reserpine is moderately effective.

In concluding, I would like to emphasize that the treatment and diagnosis of chronic headache do not belong to any one discipline or group in medicine. Rational therapy starts with the prerequisite that the physician be able to differentiate the type of headache that he is dealing with. To make the differentiation the clinician should under-

stand what is known about the underlying physiologic and psychologic mechanisms associated with chronic headache. In addition, of course, a detailed history and thorough examination are essential.

MODERATOR MERRITT: Our last speaker is J. Lawrence Pool, Professor of Neurological Surgery, College of Physicians and Surgeons, Columbia University; Attending Neurological Surgeon and Director, Department of Neurological Surgery, Presbyterian Hospital.

DR. J. LAWRENCE POOL: The cases I wish to discuss today are traumatic headaches and headaches of miscellaneous type and origin, including those due to cancer, aneurysms and brain tumors.

Post-traumatic headaches are frequent, as you well know. In my experience they are most frequent in those patients who are concerned with Workman's Compensation or litigation, or in patients with a neurotic or psychoneurotic tendency. Over the years, I have seen many patients with equally or more severe head injuries than many of the litigious and neurotic patients, who nevertheless have not had any headaches at all. As I have studied that aspect of the problem it seems to me that a very distinct feature in many cases of post-traumatic headaches is a psychological or psychiatric factor. One also sees patients with headaches after head injury due to local scalp injury, if there has been a laceration resulting in a painful neuroma. That is rare but does happen. The treatment may require local procaine injection or excision of the painful area. Subdural hematomas may give headaches of unilateral origin or location. One finds a few patients who suffer chronic recurrent headaches after head injury which are relieved by pneumoencephalogram, probably because drainage of cerebrospinal fluid alters the intracranial fluid pressure and relieves tension of adhesions upon the dural structures lining the skull. This measure is not effective in most cases, however. With these head injuries and post-traumatic headaches it is important to examine the neck for possible cervical injury. As Dr. Friedman pointed out, secondary muscle spasm may be the cause of severe headaches in the occipital region. This may be initiated by a subluxation of one vertebra on one side only, and x-rays of the neck should therefore be obtained when no other cause for these headaches can be found.

Turning to miscellaneous conditions that the neurosurgeon encounters, "temporal arteritis" was formerly seen a good deal. I think it fits

into the group that Dr. Friedman described. However, we do not seem to see such cases or treat them by surgery any more.

Tic douloureux or trigeminal neuralgia is so familiar to you that treatment by alcohol block or differential root section need not be discussed. Glossopharyngeal tic or 9th nerve pain at the root of the tongue and base of the throat is an extremely painful, paroxysmal condition that can readily be relieved only by section of the 9th nerve intracranially through a small opening. This is a simple and safe procedure. The newest treatment for trigeminal neuralgia is simple compression of the posterior root without cutting any of the pain fibers. This has proved extremely effective, so that little or no sensory loss occurs and pain is relieved. Carcinoma pain due to invasion of the base of the skull, as Dr. Baker has mentioned, may be relieved in some cases by sectioning of a number of cranial nerves on the involved side. This is a major procedure that involves sectioning the posterior root of the 5th nerve because the trigeminal innervates the dura, also the 9th nerve and also the first three cervical sensory roots on that side. All of this can be done through a simple posterior or suboccipital incision. It does reduce the pain a great deal but I have never seen it reduce the pain of cancer in the base of the skull completely. One may therefore also have to consider a unilateral lobotomy in such patients and this, combined with nerve section, has given a number of my patients relief, although not complete relief, during the months of their survival.

Intracranial aneurysms may also give pain. They may give pain referred to the eye, which is often excruciating in severity. It is paroxysmal and as a rule, feels as if, as the patients say, a knife is being twisted around back of the eyeball. Indeed, there may be no other symptoms or signs of such an aneurysm. Carotid angiography should therefore be considered in such cases, a simple and effective diagnostic test. The treatment of aneurysms is ligation of the internal carotid in the neck and trapping the aneurysm when possible by placing a clip on the vessel inside of the head at the circle of Willis. This depends on the location of the aneurysm and its nature.

Turning finally to brain tumors, we find that headaches are commonly caused by increased intracranial pressure but the presence of a tumor without pressure may also cause headaches. I would like to stress this because many of us, when we see such patients and find no

papilledema, have said that there could be no brain tumor because there was no increased intracranial pressure. However, in a recent study of acoustic nerve tumors we have found no increased intracranial pressure accompanying this type of tumor. Headache is probably due to pressure upon the tentorium or dural membranes. Postural headache, of course, may be produced by any type of brain tumor, with increased pressure, including 8th nerve tumors and intraventricular tumors.

I might say in closing then, that the treatment of many of these headaches due to intracranial lesions of the sort mentioned, particularly brain tumors, is carried out now in a much safer manner than in former days when the mortality rate from neurosurgery was high. Today we expect good results and get them.

MODERATOR MERRITT: I think it would be of value to summarize the remarks made by the members of the panel. Dr. Baker and Dr. Payne are unusually modest representatives of their specialties because they both stated that although headache could be caused by disease of the structures in which they are particularly interested, disease of these structures was not an important factor in the majority of the patients with headaches who come to the practicing physician. This statement is also borne out by Dr. Friedman's discussion. All of the speakers have stressed the importance of the thorough study of the patient from the physical side and Dr. Friedman emphasized the need for a careful psychological study. Drs. Baker and Payne emphasized that, in the treatment of these patients, relief of symptoms is not to be expected from treatment of the eye or nose if there is no significant disease of these structures. The vast majority of patients who come to the physician complaining of headache fall into one of three groups: migraine, tension headaches, or traumatic headache.

It is important to note that constant headaches are practically never a symptom of organic brain disease or organic disease elsewhere in the body. If a patient complains of headache that persists for weeks, months and years without let-up, it is probable that it is related to emotional tension.

The speakers have all stressed the importance of a thorough examination, including the eye, nose, throat, ear, the nervous system and the body in general, and that if any abnormalities are found in these examinations, they should be taken into consideration and properly treated.

In general, the treatment of the patient with chronic headaches is divided into two parts: 1) symptomatic, that is treatment of the headache when it occurs; and 2) prophylactic, the prevention of subsequent attacks.

In patients with tension headaches and practically all other types, except migraine, analgesics and sedative drugs give the best results.

Ergot preparations are the drugs of choice during an attack of migraine headache. In prophylaxis, in the prevention of recurrences, drugs are of little value. Measures directed toward the relief of emotional tension and psychotherapy to assist in the solution of every-day problems are of considerable importance. Dr. Friedman has correctly stated that this type of therapy is in the province of all doctors. If the physician gives the patient sympathetic understanding and allows the patient to do some of the talking, good results can be obtained.

We have a number of questions from the audience. Dr. Pool, is vitamin B_{12} of value in the treatment of trigeminal neuralgia?

DR. POOL: I don't think it is. It is worth a trial but our experiences with the use of vitamin B_{12} have not been encouraging.

MODERATOR MERRITT: *There are a number of questions, all dealing with the same subject, that is, what is the preparation that is used in the form of rectal suppositories in the treatment of migraine? Dr. Friedman, can you tell us what the suppository contains and how it is used?*

DR. FRIEDMAN: Cafergot suppository—the average dose is one suppository (ergotamine tartrate 2 mg. and caffeine 100 mg.) every half hour, using a total of three suppositories if necessary. We have also found that the use of the above-mentioned dosage with 0.25 mg. Bellafoline is effective in many cases where abdominal spasm and nausea are complained of.

MODERATOR MERRITT: *This is for Dr. Pool. What are your views with regard to the treatment of postoperative headache and post-spinal puncture headache?*

DR. POOL: Post-spinal headache should be treated by keeping the head down and feet elevated for 48 hours. As to the postoperative headache, most people after craniotomy, even of large size, do not complain of headaches. They may complain of them at times when

worried, tense, fatigued. You would think they would have a lot of headaches. As a rule they don't have any.

MODERATOR MERRITT: *This question is for Dr. Baker: Has it been proven that there exists a "vacuum type headache", and what is the treatment?*

DR. BAKER: There probably is a vacuum type of headache. It is one type of headache we frequently see in individuals who are exposed to rapid changes in atmospheric pressure, as in airplane flight or deep sea diving. We know that such patients will often experience a severe type of headache. The headache brought on by the pressure changes may be severe and associated with actual hemorrhage within the sinus itself. There does not seem to be any other explanation for this particular type of headache.

MODERATOR MERRITT: *Treatment?*

DR. BAKER: The treatment for it, of course, is to try to get the nose and sinuses better ventilated by the use of a vasoconstrictor.

MODERATOR MERRITT: *Dr. Friedman, is there such an entity as histamine cephalalgia? Is desensitization with histamine useful?*

DR. FRIEDMAN: A clinical syndrome consisting of periodic unilateral headaches related to the periorbital region and associated with injection and watering of the eyes and stuffiness of the nose has been described by Bing, Horton, Harris and Gardner by various names. Horton described this headache as being caused by histamine and relieved by treatment with this same drug. It is our belief that this type of cyclic cluster headache is a variant of migraine and its relationship to histamine is questionable. These headaches are usually relieved symptomatically by use of a vasoconstrictor. In a few cases, histamine, cortisone and similar types of medicaments have been of value prophylactically. Due to the fact that the duration of these headaches is usually from four to eight weeks, it is difficult to evaluate prophylactic treatment.

MODERATOR MERRITT: *We have two more questions on therapy for Dr. Friedman. What dosage of reserpine have you found useful? Is there any delayed response? Also can you comment on the use of mephenesin compounds in tension headaches?*

DR. FRIEDMAN: The average daily maintenance dose is 0.75 mg. orally. In many cases, however, patients are effectively stabilized at 0.5 mg. There seems to be no appreciable difference in the end results whether the patient is loaded in the beginning of therapy or saturation achieved slowly on a constant dose. Maximal effective action in most cases is obtained after 7 to 10 days on therapy. The drug is well tolerated and only mild side effects are noted. Sleepiness and dryness of the nasal mucosa, nausea and diarrhea are complained of in a small number of patients after maintenance is established. No evidence of addiction is noted. Since the action of reserpine taken orally is cumulative and slow, it is generally used as a preventive or prophylactic medication and not for symptomatic treatment. We have not found Tolersol to be effective as interim treatment for tension headaches.

MODERATOR MERRITT: *This question is not addressed to any of the panel, but it might go to Dr. Baker: What is the cause of early morning headaches, not in a hypertensive person but in a person who likes to sleep late?*

DR. BAKER: I will take a chance in trying to answer it. Often in the morning when a person wakes up the nose is apt to be plugged up and filled with a lot of secretion and such a condition persists until the patient starts moving around. This is particularly true if he happens to sleep in a poorly ventilated room.

MODERATOR MERRITT: *We have two final questions. I think they go to Dr. Friedman: What is the best therapy for headache and dizziness due to cerebral thrombosis and hypertensive arteriosclerosis?*

DR. FRIEDMAN: In the treatment of cerebral thrombosis we are limited to the use of the vasodilators, such as nicotinic acid and papaverine. Analgesics such as salicylates and codeine may be used for symptomatic treatment.

In the treatment of hypertensive headaches, management of the general state of hypertension is always indicated, aiming at a decrease in the blood pressure and protection of the patient against vascular insults rather than merely elimination of the headache. The available measures for lowering the pressure include psychotherapy, rest, sodium restriction, and specific anti-hypertensive drugs. Antipressor drugs used for the reduction of blood pressure include the methonium salts, diabena-

mine hydrochloride, Hydralazine, hydrogenated ergot alkaloids and Rauwolfia serpentina. Recently we have used Rauwolfia serpentina in a group of over thirty patients with hypertensive headache. This drug acts as a hypotensive agent as well as a sedative. Although not a potent hypotensive agent it has proved to be effective in reducing the severity and frequency of the headache as well as a moderate lowering of the blood pressure. We are encouraged by our results with this drug but more time is needed to prove its efficaciousness.

MODERATOR MERRITT: *We have one last question. It is posed to Dr. Friedman: "I have a headache preceding a rain. Is there any prophylaxis?" I think probably this patient should go to some country where they don't have rain. Dr. Friedman, would you give a more intelligent answer?*

DR. FRIEDMAN: I believe that Dr. Merritt's suggestion is the most effective therapy. Patients complaining of cephalalgia with temperature, humidity and atmospheric pressure changes are believed by some to suffer from a physical type of allergy. The pain is usually muscular in origin and is said to be similar to that produced experimentally by exercising a muscle which is in an ischemic condition. It is our belief that this represents another form of stress headache. The treatment is nonspecific and may include the use of vasodilators, physical therapeutic measures and analgesics.

MODERATOR MERRITT: On behalf of the Academy of Medicine, I wish to thank the members of the Panel for their contributions to this afternoon's program.

NEW YORK PATHOLOGICAL SOCIETY

*Abstracts of Papers and Discussion**

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Nodular and Fatty Glomerular Lesions in Rabbits Receiving Cortisone

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Rabbits injected intramuscularly with 15 mg. of cortisone daily developed a series of regular responses that appeared to be interrelated. These included hyperglycemia, glycosuria, polyphagia, depletion of body fat depots, neutral fat hyperlipemia with grossly milky sera, and focal nodular and fatty glomerular lesions.

The glomerular lesions were studied in detail. The initial change was an irregular dilatation of almost all glomerular capillaries. A moderate number of capillaries at the periphery of the tufts became widely dilated and ectatic. These were frequently occluded by masses of fused erythrocytes and lipid-rich, sudanophilic plasma. Cast-like concretions of a waxy material that stained deeply with periodic acid-Schiff's reagent formed in a few of these capillaries and some of these nodules were eventually extruded into Bowman's space. In addition a very few glomeruli contained large globules of fat and in some instances clusters of adipose tissue cells formed within the tufts.

Pronounced neutral fat hyperlipemia and focal glomerular lesions have not been reported in other species of animals receiving cortisone. It is suggested that the relative and absolute increase of neutral fat in the serum plays an important role in the development of the glomerular changes by causing stasis of capillary circulation within the tufts. Cholesterol feeding does not increase the incidence of nodular glomerular lesions in cortisone-injected rabbits, indicating that the cholesterol content of serum is not involved in this process.

DISCUSSION

JAMES I. BERKMAN: It would be easier to discuss this paper if the authors had said that these lesions in cortisone-treated rabbits were similar to the characteristic Kimmelstiel-Wilson nodules of diabetic glomerulosclerosis. Of course, there is a generally somewhat neglected glomerular lesion in the kidneys of diabetic patients with far advanced glomerulosclerosis to which Dr. Koss[1] has directed our attention. This is the so-called "hyaline fibrinoid" lesion and it is this which the experimental lesions so beautifully demonstrated by Dr. Stumpf resemble morphologically as well as tinctorially. The question has been raised by Dr. Koss as to what the relationship of this "hyaline fibrinoid" lesion might be to the fully developed nodular Kimmelstiel-Wilson lesion. From a study of human kidneys, it appears that there is no evolutionary relationship.

Various non-specific lesions have been reported in the glomeruli of animals with experimental diabetes. Attempts to produce a lesion resembling the characteristic nodu-

* Manuscripts received May 1955.

lar human lesion have been unsuccessful. The reason for this failure is not clear. Certainly, the diabetic state has been produced in experimental animals and maintained for a long period of time. One factor that has been missing in such animals is hypertension.

For many years, abnormalities of lipid and more recently of lipoprotein metabolism have been emphasized in the search for causes of degenerative vascular disease in diabetic as well as in non-diabetic patients. There is also less well known, perhaps, but definite evidence that there are significant abnormalities of glycoprotein metabolism in diabetic patients.

Very shortly after the demonstration that the nodular hyaline lesions in the kidneys of diabetic patients contain, in addition to protein and in addition to lipid, a high percentage of polysaccharides, it occurred to us to investigate the serum glycoproteins in such patients. It had been suggested on a number of occasions that the characteristic lesion could be accounted for on the basis of accumulation in the glomerulus of some substance from the circulating blood. It was proposed by Fahr[2] that this might be a protein. Dr. Wilens[3] pointed out that the lesions of diabetic glomerulosclerosis were richer by far in lipid than in any other form of renal disease. He suggested a relationship to circulating lipids. With my colleagues at Montefiore Hospital, Dr. Rifkin and Mr. Ross, we undertook a study of serum polysaccharides in diabetic and non-diabetic patients with and without degenerative vascular disease. One group of patients consisted of non-diabetic, non-arteriosclerotic controls. A second was composed of diabetic patients who were divided into sub-groups, depending on the presence or absence of degenerative vascular disease, and the presence or absence of renal involvement. Also included was a group of non-diabetic patients with various types of renal disease and finally a group of non-diabetic patients with arteriosclerosis. There is a significant difference between the serum polysaccharide levels in non-diabetic patients with degenerative vascular disease as compared to diabetic patients with degenerative vascular disease, whether or not it be associated with renal lesions. In diabetic patients the serum polysaccharide levels are elevated but only when clinically degenerative vascular disease is present.

One feature which distinguishes degenerative vascular disease in diabetic patients from that in non-diabetic individuals is the presence of capillary lesions which are highly distinctive if not absolutely specific for diabetes. We do not know what the relationship is between elevations of serum polysaccharide in diabetic patients and the eventual accumulation of polysaccharide substances in their glomeruli. It is conceivable that all we are measuring is a reflection of the very extensive vascular damage that occurs in diabetic patients, for it is well known that serum polysaccharides may become elevated in a variety of conditions.

I have mentioned before that the absence of hypertension is striking in experimental animals in which unsuccessful attempts have been made to produce lesions resembling those of human diabetic glomerulosclerosis. Two more slides were shown, of the kidneys of a diabetic patient with severe generalized arteriosclerosis, studied at Montefiore Hospital. The left kidney was hypertrophied, weighing 400 gm., and revealed severe diabetic glomerulosclerosis and arteriolarsclerosis. The right kidney was atrophied, weighing 50 gm., as the result of complete occlusion of the main renal artery at its origin by an old calcified arteriosclerotic plug. Not a single glomerulus in this kidney revealed diabetic lesions and only a very rare afferent arteriole revealed mild hyalinization. There are, of course, two possible directions in which the explanation for these unique anatomic findings is to be sought. The atrophic kidney either was protected from the effects of hypertension, or else something in the circulating blood which needed to reach the kidney in sufficient quantity to allow its deposition in glomeruli did not get there. Whether this might be a glycoprotein or a lipoprotein substance is, of course, unknown.

ALFRED ANGRIST: Is it conceivable that these changes represent no more than, put rather as an over-simplification, a form of atherosclerosis? In using that term I think

we can possibly effect a synthesis of the parts of the lipids, the lipoproteins and the glycoproteins in this process. I have always thought that that might be the case from a study of ordinary morphology in diabetics. We know that they do show this tendency to sclerosis, and even in Dr. Stumpf's illustrations, shown here, they are, I think, representative of what we see very commonly. Almost invariably we see the same deposition in the glomerular arterioles and smaller vessels and also very often in the glomeruli. If that be the case, it would also explain the part of heparin and the dissociation of other lipid constituents in experimental atherosclerosis in rabbits and in the human. I am wondering whether that would not bring some sense into our approach to the subject, rather than maintaining an artificial dignity by isolating diabetic glomerulosclerosis as an absolutely specific entity.

H. H. STUMPF: Is Dr. Angrist's question directed chiefly to the experimental or the human lesion, or both?

ALFRED ANGRIST: I should like very much to have the question answered: I think the experimentalist would be the one to answer it.

H. H. STUMPF: We studied these same rabbits to detect the effect of cortisone on arterial lipid deposition. The atherosclerosis produced by cholesterol feeding was inhibited by cortisone administration, and although we do not know the answer to that any more than we know the answer to the causation of the renal lesion, we feel that the imbalance in blood lipids may play a part. Oppenheim and Bruger[4] were the first to report inhibition of arterial lipid deposition by cortisone in the rabbit and their finding has been confirmed by others. I might also add that arteriolar changes were not noted in any of our animals, an additional difference between the experimental and human lesions.

ALFRED ANGRIST: I recall, and possibly some of the older members of the Society will recall, a lecture by Aschoff at the Academy when he showed similar material in the early atheroma of the aorta, in which he contended the initial lesion was brought about by that localization.

H. H. STUMPF: In the group of rabbits treated only with cortisone the blood vessels everywhere were unremarkable, except for the renal glomerular capillaries, and usually here only one, or at the most two, were appreciably altered.

MARY MARCUS: Was any study made of the polysaccharide metabolism and of infection in your experimental animals?

H. H. STUMPF: We did not attempt to study the polysaccharide metabolism. We did notice a higher incidence of infection in the cortisone-treated groups; there was a higher incidence of pneumonia, which was one of the most frequently found infections. Some degree of lobular pneumonia was two or three times as common in the first two groups of animals as in the third group treated only with cholesterol.

MARY MARCUS: Was cortisone used during the pneumonia?

H. H. STUMPF: The animals developed pneumonia in the course of the experiment; it was not severe enough to kill them. There was a higher incidence of infection in general in the cortisone-treated animals. We noted that many had conjunctivitis or dacryocystitis, and whenever they had a laceration of the skin this frequently became infected.

I would like to add that Dr. Kimmelstiel himself reviewed these slides and he was not able to relate our lesions to the human lesions. On the other hand, he did not go so far as to say that they were unrelated; he left it somewhat up in the air.

LEOPOLD G. KOSS: Dr. Berkman so eloquently exposed some of my ideas that I should keep quiet, but there is one point that I should like to make, namely, that the nodular lesion of Kimmelstiel-Wilson is a lesion that has all the characteristics of mature connective tissue, and this is not the case with the other lesion

termed exudative or hyaline-fibrinoid. The mature lesion and the hyaline-fibrinoid lesion are associated, but not necessarily so. In human diabetes the exudative lesion follows the Kimmelstiel-Wilson lesion, but not vice versa. Moreover the material found in the exudative lesion is found in the basement membrane all through the kidney; in the basement membrane of Bowman's capsule, and in what I believe is the basement membrane of the arteriole. How these lesions correlate I do not know, but I still feel that this is essentially a disease of the basement membranes in the human lesion.

There is another point which interested me greatly, and that is the relationship of lipids to these lesions. If you observe these human lesions when they are small and insignificant you do not find lipids in them. Only when they are larger and more significant in size do you find it. Therefore I express a doubt as to whether lipids have anything to do with the formation of the hyaline-fibrinoid lesion, and I wonder whether this is not just an accidental finding, and whether the lesions are not rather due to the action of cortisone than to the presence of lipids.

HENRY SIEGEL: The kidney lesions are reminiscent of fat emboli. If so, could they have originated in the infected lungs, or the marrow of these animals?

H. H. STUMPF: We checked that carefully, and also the skeleton rather carefully in these animals. We were interested in the demineralization of bone which occurs in these animals following cortisone administration, and we are fairly confident that the fatty glomerular lesions were not fat emboli. We saw no evidence of fractures, and we did not find that the incidence of the renal lesions was affected by the presence or absence of pulmonary infection.

I should say that Dr. Wilens and I definitely considered the possibility that hypertension might be the missing link in this disease process, as suggested by Dr. Berkman. According to Goldring and Chasis,[5] in man hypertension may be associated with an increased glomerular filtration fraction, possibly due to spasm of the efferent arteriole. We did not find arteriolar lesions in our animals, and there was no evidence of hypertension, whereas arteriolar sclerosis and elevation of blood pressure are frequently prominent in human diabetics.

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Mechanisms Involved in the Vascular Lesions Produced by Endotoxins

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The generalized Shwartzman reaction is being employed as an experimental model for the investigation of fibrinoid, which is deposited within the lumen and walls of blood vessels in many organs during the development of this reaction. Bilateral cortical necrosis of the kidneys, the lesion which identifies the generalized Shwartzman reaction, is caused by occlusion of the glomerular capillaries by fibrinoid.

It is postulated that fibrinoid is formed as the result of precipitation of fibrinogen derived from the circulating blood. The experimental observations on which this suggestion is based are as follows:

1. Three synthetic acidic polymers of large molecular size, with anticoagulant properties similar to those of heparin, have been shown to combine with and precipitate fibrinogen from plasma in vitro. The polymers are liquoid (sodium polyanethol sulfonate), dextran sulfate, and sodium polyvinyl alcohol sulfonate.

An intravenous injection of small amounts of endotoxin renders rabbits extremely vulnerable to the lethal effect of acidic polymer, and the typical lesions of the generalized Shwartzman reaction occur in animals receiving both materials. During the first hour after the injection of polymer, while fibrinoid deposits are being laid down in the glomerular capillaries, the fibrinogen of the circulating blood falls to extremely low levels or disappears completely.

2. Treatment of the animals with heparin, prior to the injection of endotoxin and polymer, prevents the occurrence of fibrinoid within the vessels and also prevents the depletion of fibrinogen in the blood.

3. The reaction to the synthetic acidic polymers is best elicited when the polymer is injected between one and four hours after endotoxin. During this period it has been found that the fibrinogen of the blood undergoes a qualitative alteration which is manifested by its precipitability, at low temperatures (4° C.), by heparin. This change may be due to an increased degree of polymerization of fibrinogen. Heparin-precipitability is prevented when heparin is administered to the animals before the injection of endotoxin.

It was previously shown that the generalized Shwartzman reaction is prevented by nitrogen mustard. The protective effect of HN_2 is apparently due to polymorphonuclear leukopenia. Animals in which leukopenia is prevented, by shielding the femoral bone marrow when HN_2 is administered, are not protected against the Shwartzman reaction. In contrast, the reaction produced by synthetic acidic polymers in combination with endotoxin is not affected by HN_2, regardless of the dose employed or the degree of leukopenia produced. This observation suggests that the role of leukocytes in the generalized Shwartzman reaction may be imitated, or substituted for, by the acidic polymers.

In five cases of acute "collagen disease," diagnosed clinically as either disseminated lupus or periarteritis nodosa, disseminated vascular lesions were encountered at autopsy which resembled to a striking degree the lesions of the generalized Shwartzman reaction in rabbits.

One of the acidic polymers which produces generalized fibrinoid vascular lesions in rabbits has recently been found to produce two other phenomena which are considered characteristic of "collagen diseases":

1. An intradermal injection of liquoid, accompanied by an intravenous injection of endotoxin, regularly produces cutaneous le-

sions of periarteritis nodosa, with heavy deposits of fibrinoid material in and around the walls of all small and medium-sized arteries.

2. The addition of liquoid to whole human blood produces, after thirty minutes, incubation, intracytoplasmic bodies in the polymorphonuclear leukocytes which are reminiscent of those seen in "L. E." cells.

DISCUSSION

PAUL KLEMPERER: In 1952, in a paper by Lewis Thomas and R. A. Good[1] I find the following: "The core of the problem of the Shwartzman reaction appears to be the nature and origin of the eosinophilic material which fills the glomerular capillaries. The possibility that the 'fibrinoid' material deposited in the glomerular capillaries may have originated in the circulating blood. . . ." That was two years ago, and tonight Dr. Thomas has given us the answer to the pertinent question as to what is the nature of this material and where it comes from. It is interesting to me that I have reached the same conclusions from the analysis of the tissue changes in human disease. Fibrinoid connective tissue damage associated with conspicuous vascular implication is the morphologic hallmark of this group of etiologically obscure diseases which have arrested the interest of pathologists and clinicians for more than twenty-five years. Klinge[2] and those who followed him have attempted to explain the tissue lesions by reference to their similarity with those which can be provoked by experimental hypersensitivity. I have never accepted the universal validity of this hypothesis because I believe that similarity is only partial identity and because other experimental procedures have been found to produce similar vascular lesions. It seems to me that in principle explanation of tissue lesions should first aim at an understanding of their morphogenesis. Consequently I have centered my investigations upon the endeavor to clarify the nature of the fibrinoid substances which are found in diverse maladies which seem to be clinically as well as anatomically entirely heterogeneous. One of the reasons why morphogenetic studies have been unsatisfactory in the past was the tacit belief in the identity of the deposits of fibrinoid material in obviously different diseases; this was also the reason for the belief in a unitarian pathogenesis, may it be hypersensitivity or hormonal imbalance as proposed by Selye.[3] Using the words of Dr. Thomas, the core of the question in these collagen diseases is the nature and origin of the fibrinoid, and in our attempts to attack this problem, I found that disseminated lupus erythematosus offered a key. Histochemical studies of the fibrinoid substance in systemic lupus erythematosus have led me to the conclusions which have been detailed in a paper by Gueft and Laufer,[4] published in 1954, that the fibrinoid material contains some of the protein moiety of desoxyribosenucleoprotein. Histologic observations, on the other hand, have disclosed that identical material is found within the vascular lumina. We have then circulating within the blood vessels an abnormal protein, and this abnormal protein is deposited within the vascular wall and within the connective tissue as fibrinoid material. It has seemed to me that these observations are of importance for the entire problem of the collagen diseases, or better, for all diseases characterized by fibrinoid tissue damage. An identification of the fibrinoid substance in the individual members of the group and a correlation with abnormal plasma protein components seemed to me to be the principal aim of further morphogenetic studies in human material. It was evident to me that histochemical analysis of the fibrinoid in the other maladies of the group would be far more difficult than the identification of the, so to speak, labelled fibrinoid in lupus erythematosus. It is therefore of particular interest to me that Dr. Thomas has succeeded in identifying by a method different from that of direct histochemical procedure a fibrinoid substance which can be produced experimentally, and that he has also come to the conclusion that the precursor is circulating in the blood stream. I was much impressed how carefully Dr. Thomas avoided following the conventional approach, expedient, if you wish, of investigators in this area of the so-called collagen diseases who try to produce by animal experimentation

tissue lesions simulating those of human disease, and wish to convince us that Nature is using the same method in her experiment. I believe this is not the objective of experimental pathology. Animal experiments must try to disclose the basic biologic mechanisms by which the manifestations of disease in man and animal are provoked. I am glad to see that Dr. Thomas' experimental findings lend support to the general pathogenetic principles which I believe I have found, by microscopic analysis, and which I believe hold for many of these peculiar diseases in which fibrinoid is the hallmark.

In conclusion, I might say that the role of experimental pathology and morbid anatomy was, I think, epitomized by Virchow more than one hundred years ago. The first paper of Virchow[5] on thrombosis and embolism was of purely morbid anatomic nature. It was no longer than six pages. Later, however, Virchow[6] published a report of 150 pages of his experimental findings in which he demonstrated that any material,—fibrin or blood clots, cork, and so on, introduced into the large veins was carried to the lung. In the introduction of his experimental paper Virchow wrote: "An unbiased anatomic perception permits the recognition of causal relationships. . . . The experiment is the control of the rationale found at autopsy." I believe that this combination of unbiased microscopic and anatomic perception with ingenious experiment is much more difficult now than it was in the times of Virchow. Therefore I am grateful that Dr. Thomas has shown us an experimental way by which to determine the nature of one fibrinoid and I hope he will continue so that we may have the opportunity to learn from him what other fibrinoids are, for instance that which is found in the hypersensitive animal.

HARRY P. SMITH: Since it is possible to influence this phenomenon by making a change in the leukocyte level, what about changing the fibrinogen level to see whether that would affect it? For instance, the fibrinogen level can be reduced almost to zero by chloroform poisoning, a rather drastic procedure, to be sure. It can be done by the proper use of thrombin, also a rather delicate procedure. Has that been tried?

LEWIS THOMAS: We have tried to do this, without success so far. What we would like to do is to find a way of getting rid of fibrinogen selectively without altering the other constituents of the blood. We have not tried chloroform intoxication, nor intravenous thrombin or trypsin. We did try using large amounts of streptokinase, but we never succeeded in lowering fibrinogen by more than 15 to 20 per cent and we could not demonstrate any effect from this procedure on the reaction.

HARRY P. SMITH: Thrombin intravenously is a drastic way of lowering the fibrinogen level. We found some years ago, however, that when fibrin is injected intraperitoneally into rats the fibrinogen level in the plasma falls almost to zero within a few hours. There was apparently a molecular destruction; we could never find fibrin anywhere. Perhaps that would be a procedure that could be used. I wonder whether it might be tried.

HENRY SIEGEL: About two years ago I examined some rabbits that were infected with type I pneumococcus and given cortisone somewhat as Dr. Thomas has described. These experiments were performed by Dr. Robinson. I believe Dr. Thomas knows of these experiments. Lesions were present in the kidneys similar to those described by Dr. Thomas, although they were present in only one of every 10 or 15 rabbits. About six months ago we autopsied an infant who died soon after admission to the hospital. The only positive finding was the fibrin thrombi in the glomerular capillaries similar to the rabbit lesions. I had never before observed a similar lesion in humans. A search through the older literature revealed that it has been described as occurring in fulminating infections, such as cholera and pneumococcal pneumonia. I would like to ask Dr. Thomas if the findings and mechanism that he has just demonstrated could explain this observation and I would also like to draw on Dr. Klemperer's experience as to whether he has seen similar cases.

LEWIS THOMAS: Dr. Good and I found, several years ago, that if animals were treated with cortisone in large doses for 3 or 4 days, and then given a single injection of endotoxin, they developed bilateral cortical necrosis of the kidneys with plugs of fibrinoid in the glomerular capillaries. We were never able to make this work using gram-positive organisms, but when one establishes as one does with cortisone a magnificent systemic infection with streptococcus or pneumococcus, the faintest trace of endotoxin will regularly provoke the generalized Shwartzman reaction. There are descriptions in the literature of patients with a syndrome resembling eclampsia in which sudden depletion of fibrinogen from the circulating blood occurs, and at autopsy plugs of fibrinoid material occur in the glomerular capillaries.

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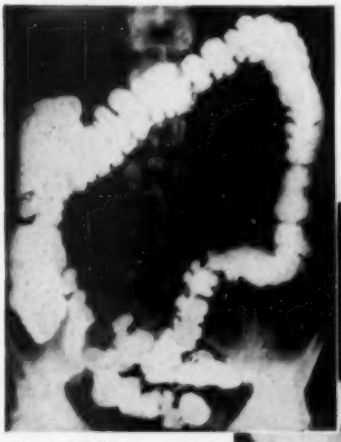

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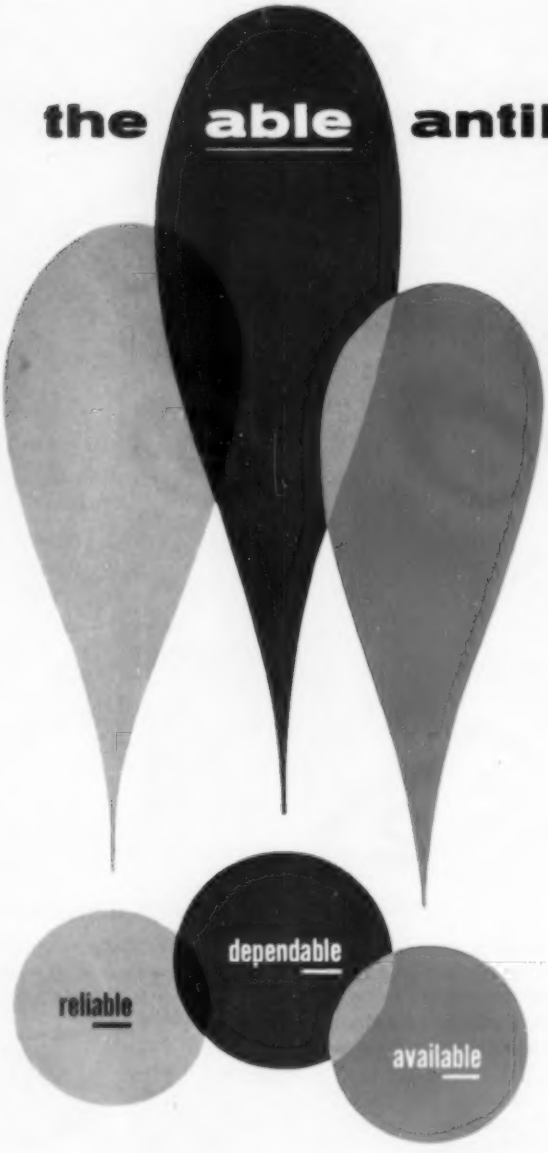

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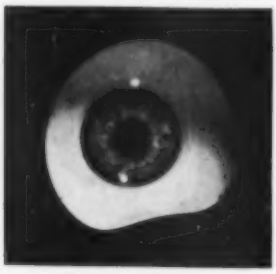

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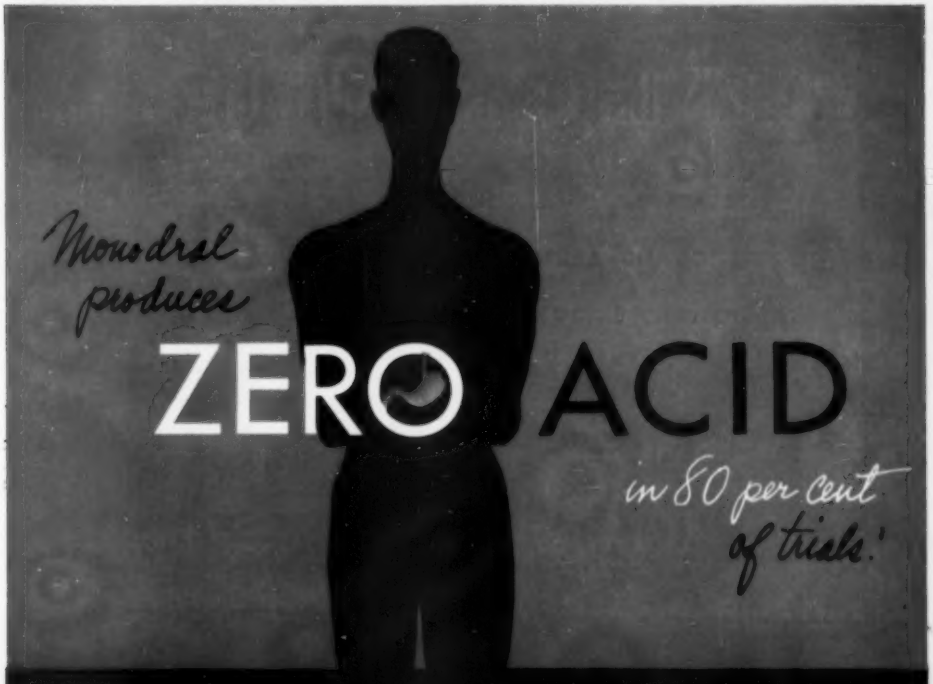

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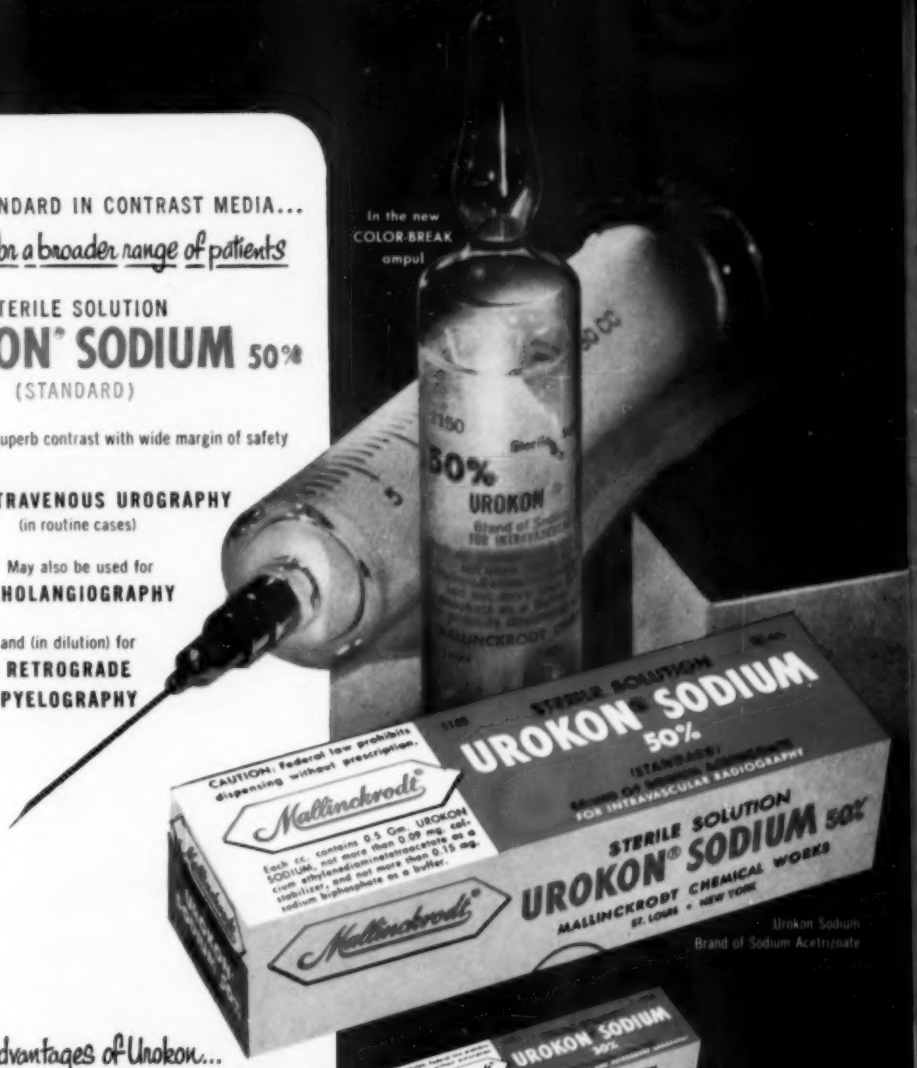
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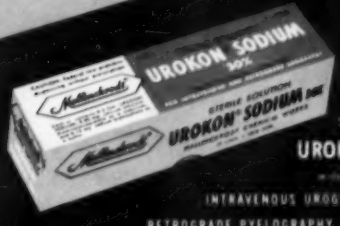

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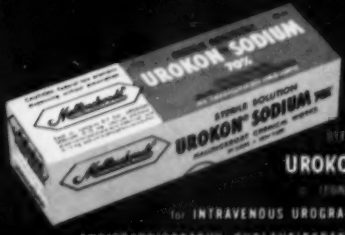

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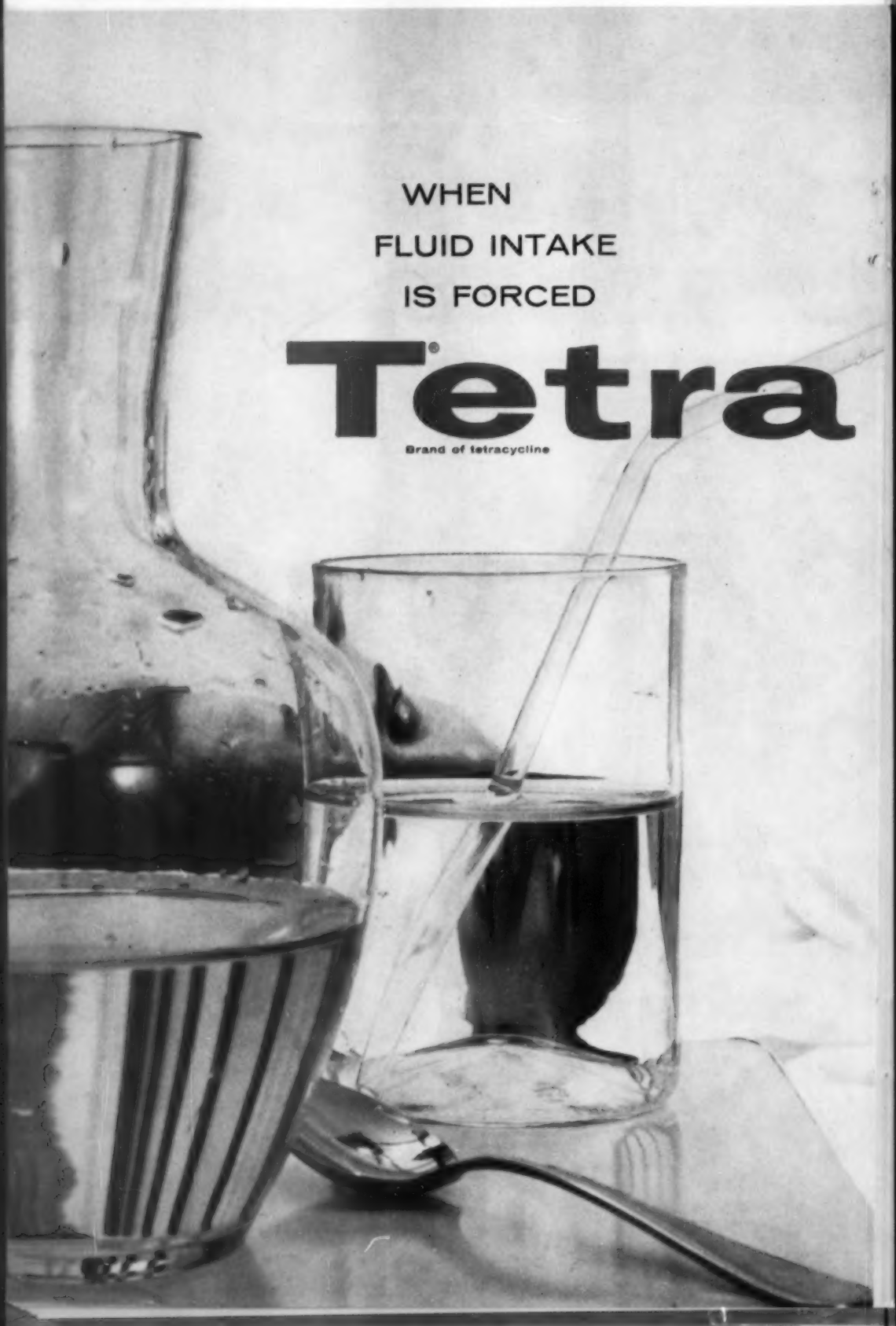
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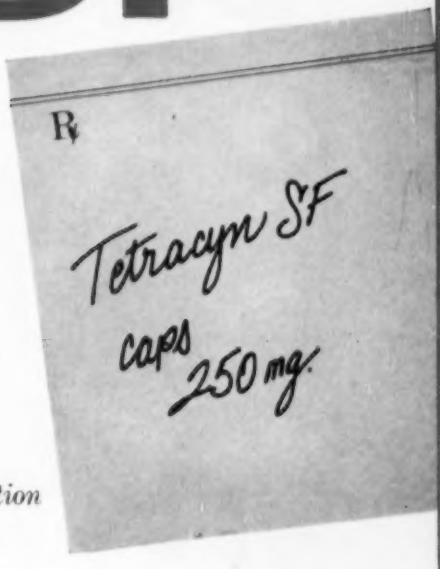

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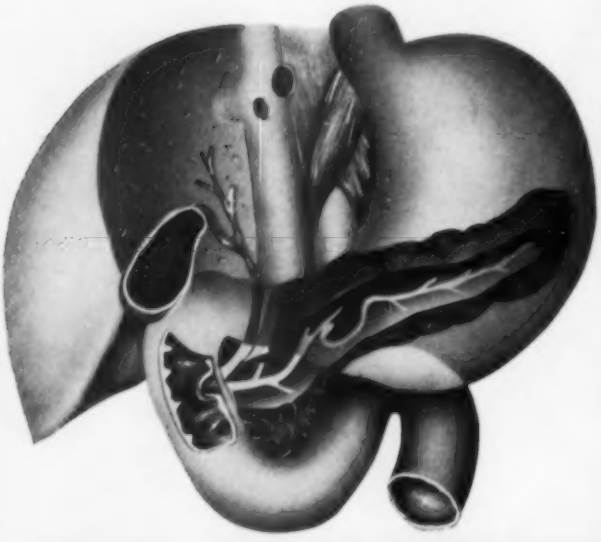

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colitis	lymphadenitis	otitis media	sinusitis
furunculosis	meningitis	pneumonia	tonsillitis

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